THE 1950 YEAR BOOK *of* MEDICINE

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DEPARTMENTS *of the* YEAR BOOK *of* MEDICINE

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Infections



PAUL B BEESON M D

PART I

INFECTIONS

INFECTIOUS DISEASES IN THE DECADE 1940 50

The development of effective chemotherapy for many of the most important infectious diseases during the past decade has brought about some striking changes in medical practice In these few years we have seen pneumococcic pneumonia change from a disease which killed one fourth to one third of its victims to a comparatively minor type of infection in which death is rare Subacute bacterial endocarditis which formerly caused death in more than 95 per cent of patients can now be cured in about 80 per cent Typhoid fever the prototype of the long febrile illness can now be brought abruptly to an end and fatalities are unusual Surgical procedures such as mastoidectomy and rib resection for empyema are seldom necessary Patients with pneumococcic pneumonia and erysipelas are comparative rarities on hospital wards Fewer papers on infectious diseases are being read at medical meetings and most of those published in medical journals deal with further successes of new antibiotic drugs Young physicians who are somewhat attracted to this branch of medicine are asking whether there is a future in it From the standpoint of developing a consulting practice there is none since few physicians today call for help in the handling of infections Professors of bacteriology are hard pressed when their students ask Why should we learn all these details when aureomycin will cure any bacterial infection anyway?

Antimicrobial Drugs

The decade has seen a continual change in the relative importance of different antibacterial agents In the early years the *sulfonamide compounds* were pre eminent and a series of new

derivatives was studied including sulfapyridine sulfathiazole sulfadiazine, sulfamerazine sulfaguanidine sulfathalidine* gantrisin® and promin® Subsequently the introduction of the antibiotics caused the relative value of sulfonamides to diminish considerably At present sulfadiazine and sulfamerazine appear to be the best agents in meningococcic and shigella infections and promin® has great value in leprosy beyond these examples one or another of the antibiotics seems to be superior to the sulfonamides in every instance Nevertheless sulfonamides are still being used widely because of their inexpensiveness It seems safe to predict however that their place will become a very minor one during the next few years

The demonstration of the effectiveness of *penicillin* and its large scale production during the late years of the war were tremendous achievements not less important was the stimulus to the search for other antibiotic agents Penicillin is unique as a pharmacologic agent in that it ha virtually no toxicity for the human being dosage can therefore be almost unlimited in size Sensitivity reactions are occasionally troublesome (seemingly especially for physician patients) but rarely constitute a serious problem It is somewhat surprising to find that penicillin is already being supplanted by some of the newer antibiotics not only for gram negative but also for gram positive pathogens While still the best agent for treatment of syphilis and gonorrhea and for most cases of bacterial endocarditis penicillin is being challenged by aureomycin and terramycin as the drug of choice for pneumococcic hemolytic streptococcic and staphylococcic infections

Streptomycin appeared to have great promise when first introduced since it seemed to complement penicillin being effective in treatment of the gram negative infections in which penicillin had little value Unfortunately its great defect is that organisms rapidly develop resistance to it consequently its value in the treatment of acute infections is limited The one infection in which streptomycin till has no equal is tuberculosis although even in this disease development of resistance is a serious problem Doubtless a better agent for tuberculosis will appear within the next decade

Aureomycin comes close to being the philosopher s stone in

infectious diseases because of its wide range of activity It acts on gram positive and gram negative bacteria rickettsiae and even some viruses If it were less expensive aureomycin would at present be the most widely used chemotherapeutic agent for infectious diseases It has minor disadvantages in that parenteral administration is not easy and troublesome nausea occasionally occurs with oral administration

A new antibiotic *terramycin* has just made its appearance (this YEAR BOOK p 36) It is similar to aureomycin in its range of activity and in early trials it appears to be about as effective and to be somewhat less apt to cause nausea Furthermore it may prove to be of value in tuberculosis

Chloromycetin first discovered and produced by a fermentation method is now being prepared synthetically It has little toxicity is well tolerated when taken orally and is effective against rickettsiae and gram negative bacteria Its great advantage over aureomycin is its effectiveness in typhoid fever but it has not shown similar promise in other salmonella infections and is relatively ineffective against the gram positive bacteria

Many other antibiotics were tried but found impractical for one reason or another Three of them *tyrothricin polymyxin* and *bacitracin* are useful for topical application but because of toxicity will probably not have wide use in systemic treatment of infections

Para aminoben oic acid was for a short time the best chemotherapeutic agent for rickettsial infections but it was soon supplanted by the even more effective aureomycin and chloromycetin

PROPHYLACTIC CHEMOTHERAPY

It is natural that administration of these potent antimicrobial agents should have been tried as a prophylactic measure These drugs are used widely to prevent development of wound infections and postoperative pneumonia Mass chemoprophylaxis has been successful in suppressing epidemics of meningococcic hemolytic streptococcic and shigella infections The long term chemoprophylaxis of rheumatic fever has been studied by several groups of physicians who used either sulfonamides or penicillin to prevent streptococcic infection and subsequent recur

rence of rheumatic activity Although there has been some dis pute about interpretation of results the general trend certainly indicates that the frequency of attacks of rheumatic fever can be diminished by chemoprophylaxis

Specific Infectious Diseases

Progress against the *common cold* has been slow Experiments with human volunteers confirmed previous evidence that the disease can be transmitted by an agent present in the nasal secretions of affected persons and that the agent is filtrable Several workers reported success in cultivating a common cold virus in the chick embryo or in other animals but none of these reports has been adequately substantiated

A series of excellent studies on *respiratory infections* was carried out by the Commission on Acute Respiratory Diseases These workers defined a spectrum of acute respiratory infections probably all due to filtrable viruses including the common cold endemic exudative pharyngitis a grippelike infection *which they called undifferentiated acute respiratory disease* and finally primary atypical pneumonia The last named disease began to attract attention about 1938 or 1939 and was extensively described throughout the past decade It probably does not represent a new disease The term primary atypical pneumonia while objectionable to many writers now seems so well established that it cannot easily be displaced The finding of cold hemagglutinins in the serum of convalescent patients provided a useful laboratory diagnostic test Recently aureomycin and perhaps chloromycetin and terramycin have been shown to be effective in primary atypical pneumonia

A considerable mass of information was added to our knowledge of *influenza* Two main strains of influenza virus were designated A and B Epidemiologic studies in this country and abroad showed that epidemics of the two strains occurred with a certain periodicity Nevertheless the factors responsible for epidemics and the location of the virus in interepidemic periods are still a mystery Influenza vaccines have had a trial The present tendency is not to use them because of the short duration of protection conferred and the unpleasant side reactions occurring in a small proportion of persons vaccinated The discovery that influenza virus agglutinated erythrocytes of various animal species

was a great help to laboratory workers in identification of the virus Of even greater importance however was the fact that it provided a tool for study of the union between a virus and its host cell indicating the presence of a receptor substance on susceptible cells Agents which inactivate the receptor substance will prevent union of virus and cell

The *prevention of air borne infection* by using aerosols and ultraviolet radiation to disinfect the air within buildings received great attention especially during the war Other procedures to minimize circulation of infectious material in air included oil ing of floors and blankets As yet however convincing proof is lacking that these measures have been developed to the point where they are practical for large scale use

Poliomyelitis has been a popular subject for study partly because of the large funds available for research The literature on this disease is enormous but as yet the mode of spread and pathogenesis are poorly understood and there is no specific ther apy A successful vaccine has not been developed Sister Kenny s teachings however illogical did afford a real stimulus and were the basis for considerable improvement in the management of patients in the acute stage In 1940 acute cases were being han dled by orthopedists who often put the patients in plaster casts! Considerable experience has been gained in the management of patients with respiratory paralysis and the indications for the respirator and for tracheotomy in such patients are being stud ied carefully at the present time

The exact cause of *rheumatic fever* remains something of a mystery but few workers would now deny that a preceding hemolytic streptococcic infection sets off the chain of events leading to development of the clinical disease Some studies sug gest that repeated infections with different types of streptococci may play a part The recent demonstration of the ameliorative action of ACTH and cortisone on acute rheumatic fever opens up a new approach to the study and treatment of this disease

Brucellosis continues to be a source of highly emotional dis pute Many weird manifestations are attributed to this disease including mental disorders multiple sclerosis and neurasthenia Acute brucellosis responds well to therapy with aureomycin and chloromycetin as do cases clinically more indolent The burden of proof is now on those physicians who ascribe psychoneurotic

manifestations and low grade fever to brucellosis solely on the basis of a positive skin test since symptoms in this group of patients are not affected by chemotherapy

The various known forms of *virus encephalitis* were investigated further particularly with respect to epidemiology Many wild birds and other animals were found to be naturally infected and several species of arthropods were found capable of acting as vectors A specific treatment is lacking

A large number of new cases of *coccidioidomycosis* occurred in military personnel stationed in the Southwest during World War II and clinical manifestations of this infection were therefore later observed in many parts of the country

Virus hepatitis was a common and important medical illness in troops in World War II in many parts of the world The term infectious hepatitis has almost entirely replaced the old catarrhal jaundice There is evidence which strongly suggests that in a very small proportion of affected persons the acute process progresses to a chronic form of liver disease with a clinical picture indistinguishable from that of Laennec s cirrhosis A similar form of virus hepatitis transmitted in blood and blood products—*homologous serum jaundice*—was also common during the war Tens of thousands of cases developed in soldiers vaccinated against yellow fever with a vaccine containing human serum contaminated with this virus Hundreds of other cases occurred sporadically in patients given blood and plasma transfusions Since no susceptible laboratory animal has been found experimental work on virus hepatitis has had to be done on human volunteers consequently progress in knowledge has been slow The weight of evidence indicates that homologous serum jaundice and infectious hepatitis are caused by similar but not identical viruses There is no specific treatment but it appears that injections of pooled human gamma globulin exert some prophylactic effect

Other diseases which received unusual attention during the war include *malaria amebiasis scrub typhus* and *filariasis*

The introduction of *DDT* provided a potent weapon to combat epidemics of typhus malaria plague and dengue

Immunization with *tetanus toxoid* proved to be a spectacular success in American military personnel during the war tetanus was almost completely eliminated

In the treatment of *leprosy* the use of chaulmoogra oil was largely abandoned Encouraging results have been obtained with prolonged courses of sulfone drugs such as promizole* and promin*

It was first shown by Australian physicians and later confirmed elsewhere that the occurrence of *rubella* in expectant mothers during the second and third months of pregnancy is likely to result in congenital abnormalities in the infant These defects include cataracts microcephaly cardiac abnormalities and deafness Considerable discussion has resulted regarding the justification for therapeutic abortion in women who have rubella during the first trimester of pregnancy

As a result of large scale field studies by members of the U S Public Health Service it was demonstrated that *histoplasmosis* is common in inhabitants of the Mississippi valley and that in endemic areas pulmonary calcifications in many instances are probably the result of histoplasma infection instead of tuberculosis

The protozoan infection *toxoplasmosis* received further study Immunologic evidence indicates that it is usually transmitted from the mother to the infant in utero In adults infection is usually asymptomatic In young infants it may take the form of an acute encephalomyelitis or may simply reveal itself as a chorioretinitis or by x ray evidence of calcification of the choroid plexus

A new disease of children *infectious lymphocytosis* was described This is often asymptomatic but there may be mild illness with fever and gastrointestinal symptoms The striking finding is the change in the peripheral blood picture appearing as an extreme lymphocytosis up to 100 000 per cu mm The disease is harmless but unless it is recognized the blood findings may cause undue concern

There was a brief flurry of interest regarding the possible widespread occurrence of *Newcastle disease* in this country based on serologic studies As pointed out elsewhere in this YEAR BOOK (p 121) it now appears that the findings were due to a technical error in the serologic test

Rickettsialpox a chickenpox like illness caused by a newly recognized strain of rickettsia appeared of all places in New York City and has not yet been reported elsewhere Some ex

cellent investigations were carried out The clinical features histopathology diagnosis and epidemiology are already clearly defined

A new virus *Coxsackie virus* pathogenic for suckling mice has aroused great interest There is clinical and laboratory evidence that it can produce a disease resembling nonparalytic poliomyelitis and epidemics of infection with this virus may have occurred concomitantly with poliomyelitis At present several laboratories are devoting full attention to this agent and its exact importance should be established in a year or two

Research in Infectious Diseases

Many good pieces of scientific investigation have appeared during the decade related to the general problem of infectious disease Among these may be mentioned the work of Avery and his associates on the substance responsible for the transformation of pneumococcic types They established that this is the property of a desoxyribonucleic acid which has properties similar to those of viruses and genes Dubos discovery of an improved method for the cultivation of the tubercle bacillus together with applications of this method by him and others has greatly facilitated research dealing with tuberculosis Wood carried out some important observations on mechanisms of resistance and has shown that the phenomenon of phagocytosis is dependent to a large degree on the physical characteristics of the surfaces on which the phagocytes rest Tillett and his associates used bacterial and chemical methods to study the characteristics of inflammatory exudates They isolated the streptococcic enzymes streptodornase and streptokinase which are capable of producing spectacular changes in the fluidity of inflammatory exudates The value of these agents in treatment of empyema hemothorax pericarditis and subarachnoid block is now under study The spectacular discovery by Hench Kendall and others of the beneficial effect of ACTH and cortisone in treatment of the collagen diseases opens up new methods for approaching some of the complex relationships between immune mechanisms and infection

Vast fields remain to be explored We know virtually nothing about the actual chemistry of infectious disease how bacterial infection makes the host ill etc We do not even under

stand the pathogenesis of the cardinal manifestation of infection—fever We still have no specific treatment for the majority of virus diseases and for the mycotic infections An embarrassing number of fevers of unknown origin still occur Undoubtedly many infectious agents are yet to be demonstrated and studied

—PAUL B BEESON

PATHOGENESIS OF INFECTIONS

Role of Allergy in Epidemiology of Common Cold is discussed by Noah Fox and George Livingston[1] (Univ of Illinois) There is considerable evidence that the common cold is an allergic response in susceptible persons to contact with a specific protein which is the cold virus or its products Some of this evidence has already been presented in the literature One author concluded from several surveys of college groups that most colds occur in a cold susceptible group the members of which have a history of more infectious disease asthma and hay fever than normal students do In one investigation it was found that 90 per cent of 51 cold susceptible persons were allergic to food That there must be other predisposing causes of susceptibility is indicated by a study which showed that although between 20 and 25 per cent of white families are free from food allergy only 12 per cent are free from the common cold and a few of these are allergic to food In another study on the relation of food allergy to colds it was noted that each of 11 allergic symptoms was associated on the average with a larger number of colds than was observed in the absence of symptoms

Two thirds of all persons with atopic allergies are sensitive to physical agents such as heat cold and effort It has been shown that histamine is liberated in the skin of normal persons when the skin temperature is decreased 20 degrees F In case of cold allergy this threshold for liberation of histamine is raised 25 degrees F The popular belief is that the common cold is initiated by chilling of the body wetting of the feet or wearing of damp clothes Response of the physically allergic person to these environmental factors may well result in an outpouring of histamine into various shock centers throughout the body particularly the respiratory tract in sufficient quantity to destroy the local defense mechanism thus preparing these tissues for acceptance of the common cold virus Of course the virus must be present

That no specific allergic antibodies are demonstrable in

(1) Arch Otolaryng 49 575 586 Jun 1949

blood of the cold susceptible person or that passive transfer has been a failure is due to lack of precise methods for demonstrating these phenomena No bacterial or infective allergy has ever been demonstrated as atopic Evidence for allergy as a factor in colds rests on the finding that persons susceptible to colds have other allergies and come from families in which allergies are present In searching for other allergies in the cold susceptible persons it must be remembered that most of these persons present the borderline or subclinical rather than the frank type of allergy

The commonest pathologic change observed in the upper respiratory tracts of cold susceptible persons in temperate climates is hyperplasia of tissues particularly along airways of the nose The person with hyperplastic tissues highly susceptible to colds rarely has a cold lasting only four to five days Almost invariably he gets a secondary infection of the sinuses lasting three to six weeks Apparently the mucosa must be injured specifically by the virus to cause these long colds

[The idea that allergy alters the respiratory mucosa, making it more susceptible to infection by the virus of the common cold seems plausible. The fact that antihistaminic drugs probably have little effect on the course of the common cold (see this YEAR BOOK p 87) does not rule out allergy as a predisposing factor Nevertheless experiments with human volunteers and observations on cold epidemics in isolated communities leave little doubt that the common cold is in some instances a straightforward virus infection —Ed]

Congenital Defects Following Maternal Rubella A relation between maternal rubella and congenital defects in the child was first suggested in 1941 when study of 78 cases of congenital cataract associated with cardiac or other lesions revealed a maternal history of rubella during pregnancy in 68 Since this initial work in Australia various congenital defects particularly cataracts cardiac malformations and deafness have been reported Further studies have disclosed that rubella in the mother during the first trimester of pregnancy is most likely to affect the child

Stuart Abel and Theodore R Van Dellen[2] (Northwestern Univ) attempted to accumulate data that might be helpful as an index of the numerical probability of congenital defects in children born of mothers who had rubella during preg

( ) J A. M A 140 1210 1212 A g 13 1949

nancy Through the facilities of a syndicated health column all such women were asked to indicate the time the ailment appeared and the outcome relative to the child

Information received in 82 letters concerning 84 babies (two sets of twins) is reported Three children were stillborn the mothers of these had rubella in the first trimester Of the 81 living children 25 were normal and 56 abnormal The principal anomalies were congenital heart disease (19) congenital cataracts (17) deafness (14) mental deficiency (7) and malformed teeth (5) Eighty seven per cent of babies whose mothers had rubella in the first trimester and 42 per cent of those whose mothers had the disease in the second trimester were abnormal one infant whose mother was affected in the third trimester had cerebral diataxia probably not related to the rubella

This method of collecting data has numerous drawbacks and limitations and any evaluation of such statistic must be made with caution The parent of a subsequently defective child is much more likely to respond Nevertheless the data cannot be disregarded because of the consistency and general agreement with several reports in the literature Appearance of congenital heart disease cataracts deafness mental deficiencies and malformed teeth in such large incidence is noteworthy and the relation to the occurrence of maternal rubella in the first trimester is striking

In the light of evidence already accumulated one might question the propriety of permitting such results to accumulate in the future At least the high percentage of congenital anomalies following maternal rubella in the first trimester is disturbing enough to warrant consideration of therapeutic curettage in these cases Evidence in this article supports those who advocate abortion although such a recommendation must always be made with caution The situation should be explained to all prospective parents who must be given opportunity to share the responsibility of deciding whether pregnancy ought to be terminated If the percentage of congenital defects even approximates figures available now the family and society in general would be better off if pregnancies in mothers having rubella in the first trimester were terminated early

[As pointed out by the authors data obtained in this way are probably weighted nevertheless the evidence that rubella during the first trimester of pregnancy is liable to cause congenital defects in the child is now conclusive The case for terminating pregnancy when the mother contracts rubella is full of religious social and psychiatric implications and no blanket solution will ever be reached It seems more sensible to see to it that young girls are exposed to rubella before they reach childbearing age —Ed]

Recurrent Meningitis Nathaniel H Schwartz and Frederick B Champlin[3] (Valhalla N Y) describe a case of recurrent meningitis in which seven separate attacks occurred all treated successfully with sulfonamides

Boy 10 was hospitalized in January 1938 because of fracture of the frontal bone extending from the right frontal sinus upward for approximately 3 in The following May he had typical meningitis the organism isolated from the spinal fluid being pneumococcus type IX In April 1939 meningitis recurred the organism isolated being pneumococcus type V Five additional attacks of meningiti have occurred one in December 1940 due to Neisseria m ningococcus one in June 1942 due to Streptococcus viridans one in November 1942 due to pneumococcus type XXXIII one in March 1943 due to pneumococcus type XIII and the last in March 1944 due to pneumococcus type XXVI When last seen in 1948 he denied having had any sequelae that might be attributed to the many attacks of meningitis Complete physical examination including neurologic evaluation was not remarkable

[A defect due to the skull fracture was probably responsible for the repeated attacks of meningitis —Ed]

Influence of Acute Infection on Course of Allergy in Children Some Clinical Observations which demonstrate that a relationship exists between infection and allergy in the child are presented by Ben F Feingold[4] (Los Angeles Children s Hosp) An allergic child with an acute infection presents a distinct pattern of allergy It may be one of two types depending on the nature of the infection The first pattern is observed in association with pertussis the infectious diseases—measle chickenpox and mumps—and the epidemic virus diseases In these diseases symptoms of allergy are aggravated during the period of invasion or the prodromal stage As these diseases approach their fastigium symptoms of allergy decrea e in severity At the peak of the illness the allergy is at a lower level than the child ordinarily experiences With convales

(3) J Ped t 35 611 617 Nov mb 1949
(4) Ib d 34 545 558 M y 1949

cence there is a recrudescence of the allergy, i e signs and symptoms of allergy not only recur but recur with greater severity and intensity than before onset of the acute infectious disease The group of diseases which produce this pattern usually confer an active immunity after a single attack and produce a leukopenia except pertussis which evokes a lymphocytosis

The second pattern is observed most commonly in association with acute infections of the upper respiratory tract rhinopharyngitis acute tonsillitis with or without adenitis adenoiditis sinusitis acute otitis or any combination of involvement of the upper respiratory tract In these infections there is no apparent change in the allergy during the period of invasion but at the height of the infection the allergy is aggravated Concomitant with the peak of the acute infectious process there is an aggravation of nasal symptoms or of pulmonary symptoms which may be manifested by acute asthma or allergic bronchitis The infections which produce the second pattern confer no immunity and call forth a polymorphonuclear leukocytosis Improvement in clinical allergy by the one group of infections and aggravation of it by the second type may suggest some studies in immunology to explain the variation in allergic response

Improvement of signs and symptoms of allergy at the peak of an acute infectious process has been reported in the literature for many years Early in the history of clinical allergy it was observed that a positive tuberculin reaction may become negative during measles A similar diminution in reactivity has been observed during other acute infections Clearing of eczema with measles is a common clinical observation Asthma has also been noted to clear with appearance of the fever of measles A positive tuberculin reaction may become negative during the paroxysmal stage of pertussis Aggravation of the allergic state by the acute respiratory infections is also cited frequently in the literature Allergic symptoms in association with this type of infection do not respond to the usual medical management for allergy Best response is observed after use of antibiotics As infection subsides allergic symptoms improve without any specific therapy directed toward the allergy

[The interrelations of allergy and infections are not yet clear but study of this problem should eventually be very fruitful —Ed.]

Tertian Malaria and Anxiety At Guadalcanal in 1943 Daniel H Funkenstein[5] (Boston) observed approximately 500 men almost all of whom had had clinical malaria and were under suppressive atabrine® treatment 0 1 Gm /day When there were no air raids a weekly incidence of approximately 10 20 cases of clinical malaria broke through the suppressive treatment However when there were nightly air raids the incidence rose to approximately 60-70 cases per week When air raids ceased incidence quickly fell Later when only sporadic attacks occurred a raid would be followed in 7 11 days by a decided increase in number of cases then a decrease until after the next air raid At the time covered by this article most air raids occurred at night and lasted one to several hours

Close correlation of incidence of clinical malaria with incidence of air raids could be interpreted on the basis that the men were often in foxholes and thus more exposed to mosquitoes While this was probably a factor it is more probable that the anxiety engendered by the air raids caused a pronounced secretion of epinephrine with squeezing of the parasites out of the reticuloendothelial system of the spleen

[A special set of Koch s postulates for psychiatry seems desirabl ! —Ed]

Adrenal Changes Produced in Rats by Infection with Bacterium Tularense and Bacterium Coli The adrenal glands respond to many infectious diseases by depletion of their cholesterol content indicating along with a falling adrenal ascorbic acid content a state of increased adrenal activity and if advanced enough adrenal exhaustion Infection with tularemia causes pathologic changes in the adrenals compatible with the pathologic picture of adrenal exhaustion However reserve of the adrenal cortex in tularemia the effect of treatment with cortical hormone and respiratory metabolism studies in animals infected with this disease have not been reported Gifford B Pinchot Virginia P Close and C N H Long[6] (Yale Univ) undertook studies to throw light on the mechanisms by which the parasite produces its characteristic disease and

(5) P y hosom, Med 11 157 139 M y J n 1949
(6) Endocn l gy 45 135 14 A gu t 1949

symptomatology in the host Bacterium coli was used to compare effects of tularemia with those produced by a less pathogenic gram negative micro organism

There was a decided increase in size of adrenals of all rats infected with tularemia There was an extreme and consistent fall in adrenal cholesterol values while ascorbic acid contents varied from normal to depleted values Treatment of infected animals with aqueous extract of cortical hormone neither prolonged survival time of recipients over controls nor prevented depletion of adrenal cholesterol Lipoadrenal extract similarly failed to prevent depletion of the glands but rats receiving lipoadrenal extract were able to maintain body temperature longer than those not receiving it Injection of Bact coli organisms produced a moderate increase in adrenal size a moderate fall in adrenal cholesterol and a moderate and consistent fall in adrenal ascorbic acid Temperature was also lowered

Adrenal hypertrophy and profound fall in cholesterol content in rats infected with tularemia probably indicates decided exhaustion of the glands by the disease Drop in cholesterol was greater than that produced by a single injection of adrenotrophic hormone On the other hand the mean value of adrenal ascorbic acid content of infected animals was higher than that observed after a single dose of adrenotrophic hormone Some levels of ascorbic acid were perfectly normal despite extremely low cholesterol values and increased adrenal size It is therefore likely that the adrenal ascorbic acid content might return to normal or near normal values in some cases of prolonged adrenal stimulation In any case it seems that this determination alone is not a reliable index of the functional state of the adrenal which has been subjected to prolonged stress

These experiments indicate that the requirement for cortical hormone is greatly increased in tularemia The animals received 10 ml water soluble extract daily or the equivalent of 4 mg compound E in addition to output of their own adrenals without meeting the demand This suggests that some published reports of failures of cortical preparations to benefit various diseases may have been the result of inadequate dosage

[Based on animal experiments such as these it has been estimated

that the human being under stress can produce the equivalent of several hundred cubic centimeters of commercial adrenal cortex extract. If so the therapeutic doses being used in such conditions as the Waterhouse Friderichsen syndrome are quite inadequate —Ed]

Inhibition of Surface Phagocytosis by Capsular "Slime Layer" of Pneumococcus Type III is described by W Barry Wood Jr and Mary Ruth Smith[7] (St Louis) Surface phago cytosis has been shown to play an important role in the mech anism of recovery in acute bacterial pneumonia Operating in absence of specific antibodies this form of phagocytosis acts



F g 1 (l ft) —El t o mc g ph f type III pneumoco cu f m f hou b oth ultu e × 10 000 lote f y slim laye that tends far be ond ma gi s of d nary caps le nd l cu es outi e f somat po t n f il.
F g 2 (ght) —Ele t n m crog aph of type I pn umococcus f m fo hou cultu e × 10 000 C mpa el ti ely na r w psul r sl m la r w th tl t of type III pne mococcu n F gu e 1
(Courte y f Wood W B Jr and Sm th M R J Expe Med 90 85 96 J ly 1949)

as an immediate defense reaction of the host and causes prompt destruction of fully encapsulated bacteria

The phagocytability of type III pneumococcus by the sur face mechanism was subjected to special study by the authors for the following reasons This organism is one of the most virulent encountered in human disease It possesses a particu larly large capsule the state of which determines its suscepti bility to phagocytosis Its capsule contains a polysaccharide with unique physicochemical properties

Results of this study based on observation of five strains of type III pneumococcus indicate that this pneumococcus is more resi tant to surface phagocytosis than any organism thus far studied Its exceptional resi tance is related to pres ence of an outer slime layer which is prominent only on highly virulent strains of the organism The slime layer which can be visualized under the electron microscope (Figs

(7) J E pe M d 90 8 96 J ly 1949

1 and 2) stains metachromatically with methylene blue and is demonstrable only on the surfaces of rapidly multiply ing cells When the slime layer is lost with aging of the bac terial population the organism is readily phagocytosed by the surface mechanism

Whether the slime layer should be considered a structure distinct from the capsule may be seriously questioned Since it is present only on surfaces of cells that are producing poly saccharide at a maximal rate it appears to represent an exten sion of the capsule in the outer portion of which the poly saccharide is less densely packed In keeping with this hy pothesis is the fuzzy appearance of the slime layer under the electron microscope and the presence of the same type specific polysaccharide in both inner and outermost portions of the envelope

It is apparent from the present studies that ability of the type III *pneumococcus to keep attacking leukocytes at a dis* tance is due to presence of the wide slime layer which extends well beyond the margin of the capsule as ordinarily seen in wet preparations

Although type III pneumococcus is the only bacterial spe cies thus far studied that possesses in the logarithmic phase of growth a sufficiently large slime layer to prevent surface phagocytosis it is not implied that pneumococcus III is nec essarily unique in this respect It seems not unlikely that other organisms particularly when growing at a maximal rate within the animal body may produce sufficient quantities of mucoid capsular material to form analogous slime layers which will temporarily protect them from surface phago cytosis

[The authors present a plausible explanation of the difficulty always experienced in serotherapy and chemotherapy of type III pneumococcic infection —*Ed*]

Hemophilus Influenzae Meningitis Possible Ecologic Fac tor In a study of H Influenzae meningitis Christopher Ounsted[8] (Radcliffe Infirm Oxford) determined certain common factors Among these were (1) an age distribution of from 3 months to 3½ years (2) the occurrence in children from large families Every patient had two or more elder living siblings aged less than 12 years Ounsted then studied two

(8) Lancet 1 161 162 J 28 1950

control series one consisted of 100 consecutive patients aged 3 months to 4 years and the other of 52 consecutive cases of meningococcic meningitis in patients of similar age distribution admitted to the same ward Because a high carrier rate had been reported among siblings of children with hemophilus meningitis the number of elder siblings was determined for the three groups and the results analyzed

The number of elder siblings aged less than 12 years in the hemophilus group differed significantly from that of the general hospital population of the same mean age however children with meningococcic meningitis had a sibling pattern identical with that of the general hospital population Therefore the distinctive pattern in the hemophilus group could not have been due to any peculiar liability in younger children of large families to meningeal infection per se On the tenuous basis of these facts the author hypothesizes that the H influenzae organism requires one or two bacterial passages through partially immune contacts before a strain is evolved that can pass the meningeal barrier

[Little contributions like this are useful in working out the pathogenesis of infectious diseases —Ed]

THERAPY OF INFECTIONS

Use of Antibiotics is discussed by Perrin H Long Caroline A Chandler Eleanor A Bliss Morton S Bryer and Emanuel B Schoenbach[9] (Johns Hopkins Univ) Until recently the problem of the proper antibiotics to use in infectious diseases was comparatively simple Either penicillin or streptomycin or both were administered This state of affairs was interrupted by the appearance of aureomycin and chloramphenicol two antibiotics with wide and effective ranges of action The physician confronted with an infectious disease which will respond to several antibiotic agents must consider a number of questions in selecting the drug to use Which antibiotic will be most effective? What is the relative toxicity of the agent in the dosage prescribed? How easily can the compound be given? What will the cost of the antibiotic

(9) J A M A 141 315 317 Oct 1 1949

TABLE 1—PRESENT DAY USAGE OF ANTIBIOTICS IN INFECTIONS*

TYPE OF INFECTION OR DISEASE	PENICILLIN G	STREPTOMYCIN	AUREOMYCIN	CHLORAMPHENICOL
Group A beta hemolytic streptococcic infections	I	III	II	—
Alpha hemolytic streptococcic infections	I	II	II	—
Str faecalis infections (group D)	II		I	—
Pneumococcic infections	I	III	II	—
Meningococcic infections	I	—	U	U
Gonococcic infections	I	II	III	III
Staphylococcic infections				
Mild or moderate	I	—	II	—
Severe	I†	—	II†	—
Acute brucellosis	—		I	I
Whooping cough	—	?	?	U
Tularemia	—	II	I	U
Typhoid	—	—	II	I
Influenzal meningitis				
Moderate	—	—	I	I
Severe	—	II+S D	I+S D	U

Key I indicates fir t ho ce II second choice III th d choice A blank s g nifies that the drug is of l ttle value. U mean that the effect is unknown S D stands for sulfadiazine.
†Comb ned therapy is used.

TABLE 2—PRESENT DAY USAGE OF ANTIBIOTICS IN INFECTIONS

TYPE OF INFECTION OR DISEASE	PENICILLIN G	STREPTOMYCIN	AUREOMYCIN	CHLORAMPHENICOL
Urinary tract infections				
Esch. coli		II	I	I
A. aerogenes		II	I	I
P vulgaris	—	II	—	I
P aeruginosa		I	—	II
Str faecalis	II		I	—
Tuberculosis	—	I	U	U
Chancroid	—	I	I	—
Friedlander's bacillus infections	—	I	U	U
Salmonella infections (food poisoning)	—		?	?
Bacillary dysertery	—		U	U
Plague	—	I	U	U
Subacute bacterial endocarditis				
Alpha streptococcus	I	—	II	—
Str faecalis (group D)	I†	I†	I†	—
Staphylococcic	I†		II†	—
Gram negative bacillary	—	I†	I†	I†
Trachoma	I	U	U	U
Surgical conditions of bowel (pre and postoperative)		I SS	U	U
Pulmonary conditions (pre and postoperative)	I	I	U	U

Key I ind cates fir t hoice II second choice III th rd choice A blank s g ifie that the drug of l ttle val e. U mean that the effect unknown. SS sta d for succinylsulfathiazole
†Combined therapy s used.

or the auxiliary costs of its administration be to the patient?

Tables 1 and 2 present in general terms the antibiotics of choice for treatment of some infections of average severity When two antibiotics are of equal effectiveness they are so listed If the infection is severe then combinations of equally effective or primarily and secondarily effective antibiotics should be used The physician should remember that sulfonamides penicillin streptomycin aureomycin and chloramphenicol all attack and damage different systems in susceptible infecting micro-organisms Intelligent exploitation of this knowledge will result in prompt and satisfying cures

Combined Therapy of Infectious Disease is discussed by Edwin J Pulaski and Hinton J Baker[1] (Brooke Gen l Hosp Fort Sam Houston Tex) Analysis of streptomycin therapy in about 2000 cases of infectious disease in U S Army hospitals strongly suggests that there is a place for streptomycin combined with penicillin and sulfonamides Although certain infections are adequately combated by streptomycin alone use of this antibiotic without supplementation has been limited by multiplication of drug fast individuals of a bacterial strain by neurotoxicity from prolonged use of adequate doses and by limitation of diffusion of the drug into cells Combined therapy aims at rapid control of infection prevention of failures due to drug fastness prevention of development of an acute into a chronic infection reduction of drug toxicity and prevention of added infection

Several species of bacteria are inhibited by all three drugs —penicillin streptomycin and sulfonamides Recently it has been demonstrated in vitro that a combination of these drugs is maximally antistaphylococcic There is evidence of enhancement of the action of streptomycin by supplementary agents against infection in animals with Friedlander s bacilli brucella and tubercle bacilli and in man with brucella and tubercle bacilli

Penicillin acts on gram negative bacteria to a greater extent than is recognized The authors have found that several species are as sensitive to penicillin as to streptomycin Bacteriostatic action in vitro is greatest in a mixture containing streptomycin penicillin and sulfadiazine Penicillin in vitro

(1) South. M J 4 765 769 Sept mber 1949

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Meningococcic infections	I		U	U
Gonococcic infections	I	II	III	III
Staphylococcic infections				
Mild or moderate	I		II	–
Severe	I†		II†	–
Acute brucellosis			I	I
Whooping cough		?	?	U
Tularemia		II	I	U
Typhoid			II	I
Influenzal meningitis				
Moderate			I	U
Severe		II+S D	I+S D	U

Key I nd cates fi t cho c II seco d cho e III th d h e A bl k g nifies that th drug of l ttle val e U mea th t th effect is nk wn S D sta ds f lfad z e

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Urinary tract infections				
Esch coli		II	I	I
A aerogenes		II	I	I
P vulgaris		II		I
P aeruginosa		I	–	II
Str faecalis	II		I	
Tuberculosis	–	I	U	U
Chancroid		I	I	–
Friedlander s bacillus infections		I	U	U
Salmonella infections (food poisoning)			?	?
Bacillary dysentery			U	U
Plague	–	I	U	U
Subacute bacterial endocarditis				
Alpha streptococcus	I		II	
Str faecalis (group D)	I†	I†	I†	
Staphylococcic	I†		II†	
Gram negative bacillary	–	I†	I†	I†
Trachoma	I	U	U	U
Surgical conditions of bowel (pre and postoperative)		I SS	U	U
Pulmonary conditions (pre and postoperative)	I	I	U	U

Key I d cat first h II d ho III th d ch ce A bl k g ifi s that th drug of l ttle v l U m that th ffe t unk own. SS sta d f s nylsulf th a ole

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(1) South M J 42 765 769 S pt mb 1949

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Pneumococcic infections	I	III	II	—
Meningococcic infections	I		U	Ū
Gonococcic infections	I	II	III	III
Staphylococcic infections				
Mild or moderate	I		II	
Severe	I†		II†	
Acute brucellosis			I	Ī
Whooping cough		?	?	U
Tularemia		II	I	U
Typhoid			II	I
Influenzal meningitis				
Moderate			I	U
Severe		II+S D	I+S D	U

Key I nd cates fi t ho ce II s c d cho e III th d cho e A bla k g nifies th t th drug s of l ttl val e U me ns that the effect i unknown S D stands for sulfad a e

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Urinary tract infections				
Esch coli		II	I	I
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P vulgaris		II		I
P aeruginosa		I		II
Str faecalis	II		I	
Tuberculosis		I	U	Ū
Chancroid		I	I	
Friedlander s bacillus infections		I	U	Ū
Salmonella infections (food poisoning)			?	?
Bacillary dysentery			U	U
Plague		I	U	U
Subacute bacterial endocarditis	—			
Alpha streptococcus	I		II	
Str faecalis (group D)	I†	I†	I†	
Staphylococcic	I†		II†	
Gram negative bacillary		I†	I†	I†
Trachoma	I	U	U	U
Surgical conditions of bowel (pre and postoperative)		I+SS	U	U
Pulmonary conditions (pre and postoperative)	I	I	U	U

Key I d t fi t ch c II cond ch III th d cho e A bl nk g lfi s that th drug of l ttle l U m a th t the ff t k w SS sta d f r yl lf th ol

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children with rheumatic heart disease were studied for three successive school years representing three rheumatic fever seasons Approximately 80 per cent had had an attack of rheumatic fever within the preceding year None was taking any prophylactic agent The children were placed in two groups division being selective only in that sex race age and economic level were carefully equalized in the two groups During the first year children in the treated group received a 50 000 unit penicillin tablet orally twice daily for five months Throat cultures taken after four months of daily penicillin on this schedule revealed beta hemolytic streptococci in 26 6 per cent of the daily penicillin group compared to 20 per cent

Percentage of Recurrences of Rheumatic Fever in Penicillin Treated Children and Controls

	School year		
	1	2	3
Penicillin treated group	3%	8%	0%
Control group 1	5%	13%	11%
Control group 2	21%	21%	19%

of the controls Because of the possibility that this regimen might be establishing penicillin fastness mode of administration was changed During the second year a five day course of two 100 000 unit penicillin tablets five times daily was repeated five times at varying intervals throughout the autumn winter and spring Since results of the second year indicated that maximal reduction in incidence of throat cultures positive for hemolytic streptococci could be maintained at least three weeks following oral administration of this quantity of penicillin dosage schedule for the third year was modified as follows Penicillin was given the first school week of every calendar month throughout the third school year Each course of penicillin amounted to 5 600 000 units (two 100 000 unit tablets four times daily for seven days)

Penicillin given every fourth week for seven days completely eliminated group A hemolytic streptococci in every month but two High incidence in February was not surprising since this month was the peak for both the second and third years Penicillin sensitivity assays were conducted on the 274 strains of beta hemolytic streptococci isolated during

appears to potentiate the bacteriostatic action of streptomycin and sulfadiazine Sub bacteriostatic concentrations of the three drugs in combination effect a lag in emergence of streptomycin resistant strains It is significant that drug resistance ultimately develops regardless of the combinations used unless there is complete bacteriostasis

The authors conclude that an optimal bacteriostatic effect against streptomycin susceptible bacteria is produced by a combination of three antibacterial agents even when one of the agents alone is apparently ineffective

[Undoubtedly combinations of antimicrobial drugs are sometimes more effective than the use of a single antibiotic. The subject is now receiving intensive study both in the laboratory and in the clinic Disadvantages include greater expense greater likelihood of toxicity and the possibility that two agents may occasionally interfere with, rather than enhance each other s effect.—Ed]

Oral Penicillin Prophylaxis of Recurrences of Rheumatic Fever Interim Report on Method after Three Year Study Although penicillin is an unsatisfactory therapeutic agent for rheumatic fever it should be excellent for prophylaxis of recurrences because of its ability to control hemolytic streptococcus in vivo Since penicillin like the sulfonamides apparently fails to influence onset and course of an attack of rheumatic fever if given after the preceding hemolytic streptococcic infection it becomes mandatory to eliminate hemolytic streptococci entirely during the period preceding a possible recurrence Kate H Kohn Albert Milzer and Helen MacLean[2] (Chicago) present results of a three year study to determine optimal oral dosage of penicillin for elimination of hemolytic streptococci from throats of children who have had rheumatic fever and to note effect of this elimination on recurrence rate of rheumatic fever

All children were living in their own homes and attending public school Therefore they presented a different problem from that of children residing in the controlled atmosphere of the hospital or convalescent home not only because they were exposed to infections prevalent in the community but because medical care especially of seemingly mild upper respiratory infections was frequently neglected or delayed A total of 126 children attending a special public school for

(2) J A M A 142 025 J 7 1950

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the second and third years of study Sensitivity figures were within the usual range of nonresistant strains

Percentage of recurrences of rheumatic fever during the three year study is shown in the table Since recurrence rate of rheumatic fever was zero in the penicillin treated group com pared with 11 and 19 per cent in control groups 1 and 2 dur ing the third year results encourage continued study

[The effectiveness of ch moprophylaxis of recurrent attacks of rheu matic fever continues to be demonstrated Trial of some form of chemo prophylaxis should be considered for any child who has had rheumatic f ver —Ed]

Inhalation of Penicillin Dust Its Proper Role in Manage ment of Respiratory Infections Aerosolized penicillin (the mist form produced by forcing oxygen or air through an aqueous solution of the antibiotic) was introduced for treat ment of respiratory infections in 1944 The agent was ab sorbed into the blood stream via the lungs Usefulness of the procedure was confirmed by a number of investigators It oc curred to L R Krasno (*Univ of Illinois*) *and Paul S* Rhoads[3] (Northwestern Univ) that if a simple device could be made which would get powdered penicillin to the site of respiratory infection it might be more effective than nebulized penicillin because there would be a maximal concentration of the antibiotic at the point where it was needed Other advan tages would include simplicity and inexpensiveness stability of the preparation at room temperatures avoidance of pain and inconvenience associated with injection of penicillin sustained local action over several hours and the probability of less local irritation than with nebulized penicillin Use in conjunction with parenteral therapy would shorten hospitalization or home confinement

The desired advantages have been achieved with two de vices a mask which permits simultaneous inhalation of peni cillin dust through no e and mouth and a small plastic housing for a small cartridge of penicillin fitted with separate detach able mouth and nosepieces The plastic device is used at present

The authors have given penicillin dust therapy to about 1 000 patients with various types of respiratory infections Bacterial infections of the nasopharynx paranasal sinuses

(3) Am Pr ct 3 649 653 July 1949

nasal mucosa larynx and trachea of fairly recent origin respond well to this form of treatment Bronchiectasis and sinusitis of long standing are greatly relieved in most cases but in many instances are kept under control only so long as therapy is continued It is questionable whether bronchiectasis could be cured by it in the absence of other measures Nevertheless the authors have a number of patients who after initial therapy have required little or no penicillin dust to *maintain initial improvement* The course of ordinary colds is strikingly shortened by prompt use of penicillin dust inhalation Blood levels of penicillin ranging from 0 03 to 1 92 units/cc serum about one hour after inhalation of 100 000 units and declining slowly over the next four hours have often been obtained Incidence of local reactions such as redness or swelling of the tongue and inside of the cheeks was about 5 per cent

Penicillin dust is a surface application which quickly inhibits growth of most gram positive and some gram negative bacteria so that cultures taken 24 hours after three or more doses given at intervals of a few hours reveal almost complete disappearance of the organisms However in many instances unless more treatment is given these organisms reappear in cultures Therefore if the patient has severe systemic manifestations of infection intramuscular administration of penicillin and/or oral administration of sulfonamides should also be used

In bronchial asthma with infectious bronchitis therapy must be directed toward the allergic as well as the infectious component of the disease Inhalation of penicillin dust helps control the severe paroxysms by controlling the infectious element Penicillin inhalation is adjunctive therapy and its exclusive use is disappointing The pneumococcus organism readily disappears from the upper respiratory tract after inhalation of penicillin dust Nevertheless pneumonia should be treated with penicillin intramuscularly or intravenously or with streptomycin if due to a streptomycin sensitive organism If there is concomitant infection of the upper respiratory tract as is often the case use of penicillin dust in addition may be helpful Both parenteral and inhalation penicillin ther

apy is the logical approach to lung abscess if the organism is gram positive

Reactions to penicillin dust therapy were those of transient irritation of the tongue and posterior pharyngeal wall No generalized urticaria no angioneurotic edema or no edema within the respiratory organs was noted

The question is raised whether favorable clinical results noted with penicillin dust can be attributed primarily to topical action of the dust its systemic action or a combination of both A complete answer awaits further investigation as to distribution of penicillin dust in the respiratory tract Clinical results indicate that the inhaled penicillin dust arrives at the site of a lesion one way or another in therapeutic quantities

Penicillin dust inhalation in some instances is the only treatment required but often this treatment should be used in conjunction with one or more of the commonly accepted means of combating infection of the upper respiratory tract such as vasoconstrictors bronchodilators antihistaminics removal of allergens surgical drainage and the like For deep seated infections with severe systemic manifestations it should be used in conjunction with parenterally introduced penicillin or sulfonamides

Aureomycin Plasma Concentrations Influenced by Aluminum Hydroxide In an early report on the use of aureomycin it was suggested that aluminum hydroxide might alleviate the accompanying nausea and vomiting The practice of administering aluminum hydroxide with aureomycin has become widespread and until recently its advisability has not been questioned It occurred to William P Boger Walter V Matteucci John O Beatty and Herbert M Baganz[4] that combined administration of aureomycin hydrochloride and aluminum hydroxide might result in (1) chemically neutralizing aureomycin and inactivating it or (2) adsorbing the antibiotic agent on aluminum hydroxide so that aureomycin would not be available for absorption from the gastrointestinal tract In either event it appeared likely that lower plasma concentrations of aureomycin would be observed when it was given with aluminum hydroxide than when aureomycin was administered alone

(4) J Philadelph Gen Hosp 1 37 Ja y 1950

Testing this hypothesis revealed that a single dose of 30 ml (six patients) or repeated doses of 15 ml aluminum hydroxide every six hours (six patients) resulted in reduction of aureomycin plasma concentrations to one fourth or one eighth those observed after administration of aureomycin alone

It is concluded that although aluminum hydroxide alleviates nausea and vomiting resulting from aureomycin this result is obtained at the price of destruction or adsorption of a significant quantity of the antibiotic agent

[Frequent feeding seems about the best way to avoid nausea from aureomycin.—Ed]

Aureomycin Therapy in Pulmonary Involvement of Pancreatic Fibrosis (Mucoviscidosis) According to Harry Shwachman Allen C Crocker George L Foley and Paul K Patterson[5] (Boston) the common notion that pancreatic fibrosis is rare and that the immediate prognosis is always poor is no longer tenable Another misconception is the view that the disease is solely one of the pancreas and that involvement of other organs chiefly lungs and liver is secondary to the disorder in the pancreas Farber described the generalized nature of the disease and introduced the term mucoviscidosis to signify the essential alteration in mucus secreting glands as a primary defect Though there is great clinical variation in the disease the frequency of early pulmonary symptoms is striking A constant feature is the laboratory finding of Staphylococcus aureus in the nasopharynx

Management of a patient with pancreatic fibrosis involves consideration of replacement therapy in the form of pancreatin use of protein hydrolysates administration of a high caloric diet with some restriction of fat and a liberal supply of vitamins including water miscible vitamin A The pulmonary infection presents a grave therapeutic problem Favorable clinical response to aureomycin of a patient aged 3 with pancreatic fibrosis and extensive pulmonary involvement suggested to the authors that further use of the drug was warranted

Thirty five infants and children have now been treated and followed for at least two months after institution of aureomycin therapy Early in this study aureomycin was used

(5) New England J Med 241 185 19 Aug 4 1949

only to replace aerosol therapy with penicillin or streptomycin or both However as experience was gained the drug was ad ministered more liberally even to patients with minimal pul monary signs who at the time were not receiving antibiotic therapy At first the drug was given four times daily, but more recently it has been given in divided or even in single daily doses An effort was made to provide the minimal effective amount for each patient This is roughly 20 30 mg /kg body weight or 125 250 mg daily in divided or single doses for infants and 250 750 mg a day in two or three divided doses for children

The most striking effect of therapy was the consistent amelioration of cough dyspnea and respiratory distress Fever if present was likewise favorably affected Response was rapid a change usually occurring within two or three days In some cases the parents stated that for the first time in weeks the child slept through the night without cough This excellent response was observed in 31 of the 35 patients Flora of the nose and throat was essentially unchanged in many pa tients after they had received aureomycin Clinical improve ment bore no relation to bacteriologic improvement the for mer being commonly and the latter only rarely observed Nau sea and vomiting frequent side effects of aureomycin in adults were rarely encountered in these patients

Aureomycin was discontinued in several patients after varying periods Within three to seven days a relapse oc curred particularly in those with extensive pulmonary in volvement Readministration of the drug resulted in improve ment

Since aureomycin is effective in small oral doses and pos sesses few undesirable properties it may become a useful adjunct to the other therapeutic agents used in pancreatic fibrosis The drug can be given continuously over a long pe riod without untoward effect Symptoms return promptly when it is discontinued

Terramycin, a New Antibiotic, is described by A C Fin lay, G L Hobby S Y Pan P P Regna J B Routien D B Seeley G M Shull B A Sobin I A Solomons J W Vinson and J H Kane[6] (Brooklyn) Streptomyces rimosus

(6) Science 3 85 Jan. 27 1950

a new actinomycete was isolated from soil When it was grown on plates containing nutrient agar and when a variety of bacteria including certain gram negative enteric organisms aerobic spore formers and gram positive cocci were streaked across these plates growth of the test organisms was inhibited in the vicinity of the colony of the actinomycete From broth cultures of this organism a crystalline antibiotic named terramycin was isolated

Crystalline terramycin was found to inhibit growth of Aerobacter aerogenes Klebsiella pneumoniae Escherichia coli Salmonella typhosa Salmonella paratyphi Salmonella schottmulleri Salmonella pullorum Shigella paradysenteriae Bacillus subtilis Staphylococcus albus Staphylococcus aureus Proteus sp Pseudomonas aeruginosa and Brucella bronchiseptica It proved effective when given both orally and parenterally to infected mice and had a low degree of toxicity in animals

[Terramycin appears to be an important new drug It is very similar to aureomycin in range of activity It may hav some advantage in being less likely to cause nausea though gastrointestinal symptoms are not rare There will be a rash of clinical reports on this drug during the coming year —Ed]

Polymyxin Effective in Treatment of Pyocyaneus Sepsis Report of Case Robert S Wallerstein (New York City) and Emanuel B Schoenbach[7] (Johns Hopkins Univ) report the successful use of polymyxin in a patient in whom septicemia followed a protracted labor which ended with cesarean section and was complicated by a renal shutdown The pyocyanic organism showed extreme resistance to streptomycin penicillin and sulfadiazine clinically and in vitro However sensitivity to polymyxin was demonstrated in vitro and polymyxin B (aerosporin) therapy resulted in prompt recovery Spontaneous recoveries from pyocyanic sepsis are rare and run a long and stormy course this patient had deteriorated steadily until polymyxin therapy was initiated

Drug fever has not been noted to accompany use of polymyxin D but has been encountered with polymyxin B In this patient during the first five days of therapy temperature fluctuated between 101 and 103 F (Fig 3) During a one day interruption in therapy while a fresh supply of the drug

(7) J Mt Sin H p 16 190 196 Sept Oct. 1949

DAY OF ILLNESS 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

TEMPERATURE 105 104 103 102 101 100 99 98

AREAS IN BOXES POLYMYXIN 160 MG/DAY (40 MG q6h I.M.)

BLOOD CULTURE
URINE CULTURE
STOOL CULTURE
BLOOD UREA NIT 125 121 127 102 69 47 30 25 38 44 59 23 29 27 26 33 28
W.B.C ( ) 20.9 15.9 9.8 8.3 9.2

Fig 3—Data c g 6 t f weeks (Co te y f Wall t R S and Scho nbach E B J Mt S a Ho p 16 190 196 Sept Oct 1949)

was being obtained temperature fell below 100 F On re newal of therapy for five additional days temperature again rose to 101 102 F It promptly fell after cessation of therapy and remained normal

Use of polymyxin in the face of unresolved and severe acute renal damage is significant The risk was believed to be justified because of the serious prognosis in the absence of such therapy With a daily measure of urinary output blood

urea nitrogen and urinary albumin it was possible to administer polymyxin without apparent aggravation of the already existing renal damage

Tracheobronchial Aspiration with Urethral Catheter Method of Treatment and Prevention of Asphyxial Hazard in Medical Diseases and Emergencies Leonard Cardon[8] (Northwestern Univ) emphasizes that obstruction of the airway by accumulating tracheobronchial secretions is a frequent but usually unrecognized complication of many conditions that the internist and general practitioner see in daily practice Asphyxia due to retained tracheobronchial secretions arises so often and may have such serious consequences if not corrected immediately that the physician should be prepared to treat it without delay In most cases aspiration of the tracheobronchial tree through a nasally introduced urethral catheter can be undertaken safely and effectively by any internist or general practitioner Cardon has successfully used this device in patients with pneumonia acute bronchiolitis superimposed on chronic pulmonary disease acute cerebral damage chest injury acute pulmonary edema morphine depression acute myocardial infarction and many other diseases He believes that tracheal rales should be regarded as a sign not that death is imminent and inevitable but that accumulated tracheobronchial secretions must be aspirated without delay The attending physician must be ready to undertake this lifesaving measure without depending on assistance of a specialist

In most patients effective aspiration can be accomplished through a catheter passed through the nose and inserted blindly into the trachea The technic can be mastered quickly The only equipment needed an ordinary urethral catheter and an electric suction machine is readily available

TECHNIC —A new or fairly stiff size 16 F catheter is passed through the nostril into the glottis and trachea and connected by a glass tube to the long rubber tube leading to the vacuum bottle of an electric suction machine Moistening the catheter in water provides adequate lubrication without making it too slippery to handle Ordinarily no special maneuvers are needed to insert the catheter through the nostril into the trachea On occasion however it may be necessary to dorsiflex the head and neck slightly and/or pull out the tongue The catheter (after nasal or oral insertion) is passed

(8) J A M A 14 1039 1044 Ap 8 1950

quickly into the trachea at the moment of inspiration when the glottis is open Entrance into the glottis is usually signaled by a hollow cough and increase in cyanosis and restlessness often accompanied with momentary suspension of breathing due to glottic spasm Breathing when resumed is whistling and stridor like Whether the catheter has entered the trachea can be determined by inserting its outer end in a glass of water and watching for bubbles As soon as the catheter is known to be in the trachea it is rapidly inserted as far as possible and suction is applied as the catheter is drawn up and back several times Except in deeply comatose patients coughing usually occurs when the catheter touches the carina Coughing is desirable during suction because it raises retained secretions into large bronchi and trachea where they can be reached by the catheter

Contraindications to endotracheal catheterization include pronounced local disease in the larynx alarming glottic spasm and obstruction or gross purulent infection in nasal passages

[This simple procedure may be lifesaving in many situations The physician who accepts responsibility for care of severely ill patients should be ready to carry it out —Ed]

Management of Patients with Tetanus Some Clinical Experiences with Various Muscle Relaxing Agents Harold E Godman and John Adriani[9] (Charity Hosp of Louisiana) describe their experience with muscle relaxing agents and sedative drugs in 70 patients aged 8 days to 93 years with tetanus of various degrees of severity

Twenty five patients were given either procaine and thiopental sodium or procaine and tribromoethanol Phenobarbital was given intramuscularly or orally in 1 3 gr doses and intravenous infusion of 0 1 per cent solution of procaine hydrochloride in 5 per cent dextrose in distilled water was started Solution of thiopental sodium either 2 5 per cent or less was kept in readiness When signs of toxicity or hyperirritability occurred procaine administration was reduced in rate or stopped for a period If symptoms of toxicity did not disappear thiopental sodium was administered intravenously in the amount necessary to control restlessness and excitement When it became necessary to administer thiopental sodium almost continuously infusion of procaine hydrochloride was discontinued Treatment was given on an average of once daily for 30 minutes to 2½ hours Some muscle relaxation and

(9) J A M A 141 754 756 Nov 12 1949

diminution in sensitivity to stimulation was produced However this effect was not long lasting and supplemental sedation was soon necessary When thiopental sodium alone was given the effect wore off in an average of 30 minutes Tribromoethanol 50 mg /kg body weight given as supplemental sedation between treatments with procaine produced muscle relaxation which in many instances lasted longer than that produced by the procaine thiopental sodium combination Of the 25 patients treated 5 died It was concluded that intravenous administration of procaine is hazardous requiring constant attention and careful observation

Phenobarbital and amobarbital sodium were given to 22 patients Phenobarbital proved to be a good sedative but was ineffective in controlling muscle rigidity and spasm in even moderately severe tetanus Amobarbital sodium given intravenously was effective in relieving an acute tetanic spasm but was not so effective as tribromoethanol or a combination of tribromoethanol and procaine in general control of muscle rigidity and spasm

Ten patients were given tribromoethanol without procaine All received phenobarbital but tribromoethanol was relied on for control of muscle rigidity and spasm A dose of 50 mg /kg body weight rectally was given as often as needed average interval being three to four hours in severe tetanus It was concluded that the drug is effective in controlling muscle rigidity and spasm However varying degrees of respiratory depression and rectal irritation often occur

Three patients were given chloral hydrate as a sedative Fairly severe respiratory depression developed in all and two died with tetanic spasms Curare in oil was used in two patients Results are not always predictable and the treatment has many disadvantages

Eight patients were given tolserol* The dose for children was 62 5 750 mg but the one adult received up to 3 500 mg All were given 1/2 gr phenobarbital once twice or three times daily This treatment proved effective in seven patients with moderately severe tetanus but ineffective in the patient with severe tetanus It was concluded that the combination of phenobarbital and tolserol* is highly satisfactory in controlling muscle rigidity and spasm in moderately severe tetanus

and that with its use less difficulty is encountered in keeping respiratory passages free from secretions Pulmonary complications were observed in only one patient

Because tetanus varies in many respects in different persons evaluation of results with various forms of therapy is difficult All patients with tetanus require constant attendance and careful observation because the course of the disease may change abruptly In all cases of tetanus except the mildest form in which diagnosis is actually questionable early tracheotomy is recommended to eliminate possibility of upper respiratory obstruction and to facilitate elimination of irritating and obstructing secretions from lower respiratory passages In many patients the amount of sedation required is decidedly reduced after tracheotomy Control of muscle rigidity and spasm is considered essential No one antispasmodic agent has proved entirely satisfactory and all have certain disadvantages

[A useful evaluation of muscle relaxing drugs by competent observers I have used tolserol® in a few cases of tetanus and have been favorably impressed with it.—Ed]

PNEUMOCOCCIC INFECTIONS

Treatment of Pneumococcic Meningitis with Penicillin Study of 125 Consecutive Cases with 73 Per Cent Recovery, is reported by Emanuel Appelbaum Jack Nelson and Michael B Albin[1] (New York City) Patients in the series were seen between June 1944 and October 1948 A primary focus was established in 78 A definite focus in the ear mastoid or both was found in 36 There were six instances of definite sinusitis In 27 patients presence of pneumonia was regarded as the probable primary focus There were seven cases of head injury with fracture through a sinus mastoid or base of the skull in five In two patients meningitis followed cellulitis of the face There remained 47 in whom meningitis was preceded either by no obvious illness or by a simple upper respiratory infection Many strains of pneumococci were represented An apparent relation between meningitis due to type III and an

(1) Am J M Sc 218 260 264 September 1949

otitic infection was shown by the fact that of 15 cases due to this type the primary focus was otogenic in 11

Penicillin was administered intrathecally in all but two instances In addition all patients were treated with penicillin intramuscularly and most of them received also a sulfonamide usually sulfadiazine Schedule of penicillin therapy finally evolved was as follows Children up to age 4 were given three to five intrathecal injections of 25 000 50 000 units each and 400 000 units intramuscularly daily for 7 10 days Older children and adults were given three to five intrathecal injections of 50 000 100 000 units and 800 000 units intramuscularly for 7 10 days In eight cases an attempt was made to treat the patient with penicillin intramuscularly but not intraspinally these patients received sulfadiazine also Satisfactory response was obtained in only two of these the remaining six failed to respond requiring additional use of intrathecal penicillin

There were 92 recoveries and 33 deaths in the series Prognosis was decidedly worse for older age groups Reactions attributable to intrathecal administration of penicillin were encountered in several instances The outstanding irritative symptoms were pyrexia delirium and convulsions which occurred a few hours after intrathecal injection of the drug This type of reaction was induced in three instances by dosages of 50 000-100 000 units and in one instance by an inadvertent injection of 500 000 units In addition there were four instances of a secondary meningitis due to Bacillus pyocyaneus introduced during intrathecal administration of penicillin

It is clear that adequate use of penicillin intrathecally and intramuscularly was highly effective in treatment of most cases of pneumococcic meningitis Though it could not be definitely stated that larger intrathecal doses of penicillin were necessarily more effective than smaller ones the authors feel that use of larger doses contributed materially to recovery of many patients Contrary to general belief the large intraspinal doses of the drug were well tolerated with few exceptions It is unwise at present to rely solely on intramuscular use of the antibiotic However treatment without intrathecal penicillin deserves further investigation

[The argument about the value of intrathecal administration of peni

cillin in pneumococcic meningitis goes on and on I believe intrathecal injections are beneficial To avoid meningeal irritation I never give more than 20 000 units intrathecally and dilute this in at least 5 cc saline —Ed]

Treatment of Pneumococcic Pneumonia with Aureomycin Though penicillin is extremely effective in treatment of pneumococcic infections the relative value of aureomycin should be determined for several reasons There is a possibility that the low fatality rate obtained with penicillin may not represent the lowest possible rate obtainable and that better results may be obtained with aureomycin Aureomycin if effective can be used in patients who have become hypersensitive to penicillin Since aureomycin can be detected constantly in serum after it has been taken orally whereas this is not always true of penicillin administered orally aureomycin may be preferable when oral medication is desired

Harry F Dowling Mark H Lepper Hugh H Hussey Eston R Caldwell Jr and Harold W Spies[2] (Washington D C) used aureomycin in treatment of 131 patients with typed pneumococcic pneumonia There were two deaths One woman 58 died 30 minutes after a single dose of aureomycin another 85 who had had hemiplegia for six months before pneumonia developed and was in an advanced stage of malnutrition on admission died 20 hours after the first dose of aureomycin

A case fatality rate of 1 5 per cent obtained in these 131 typed cases of pneumococcic pneumonia compares favorably with a rate of 5 2 per cent among 686 patients treated in previous years with penicillin This is shown especially well in a comparison of patients arranged according to age groups treated with sulfonamides penicillin and aureomycin In aureomycin treated patients who recovered temperature dropped more rapidly than in penicillin treated patients The authors conclude therefore that aureomycin is at least as effective as penicillin in pneumococcic pneumonia

[It is hard to believe that any drug could work better than penicillin in pneumococcic pneumonia yet this is an impressive report Confirmatory experience is given in the next article —Ed]

Aureomycin Treatment of Pneumococcic Pneumonia *Clinical and Laboratory Studies on 33 Patients are reported* by Thomas M Gocke Harvey S Collins and Maxwell Fin

( ) J Lab & Clin Med 35 215 219 February 1950

land[3] (Harvard Univ) Patients were aged 13 75 with a preponderance in the older age groups and the usual predominance of males over females Eight patients including 4 with bacteremia were 65 or older Pneumococci of 16 different types were represented and two thirds of the cases were due to types I VIII exclusive of type VI Six patients had acute alcoholic intoxication when admitted

Aureomycin sensitivity of the 32 different strains of pneumococci tested ranged from 0 39 to 3 12 μg /cc most being completely inhibited by less than 1 μg /cc None of the patients had previously received any serotherapy sulfonamides or antibiotics The first dose of aureomycin was usually given on or before the fifth day of illness and all patients were acutely ill at the time Pneumococcemia was found in pretreatment blood cultures in one third of the patients Most patients were given aureomycin by mouth in doses of 1 Gm every four or six hours or of 0 5 Gm every four six or eight hours The dose in 9 of 16 patients who received 1 Gm was reduced to 0 5 Gm after temperature reached normal and condition improved Total oral dosage of aureomycin ranged from 5 5 to 46 5 Gm given over 2 15 days Parenteral therapy was used in six patients in two 100 mg aureomycin was given intravenously and intramuscularly every two to four hours and in four 500 mg was given intravenously once daily in 1 or 1 5 L isotonic sodium chloride solution or 5 per cent dextrose solution in distilled water

Aureomycin given orally or intravenously was highly effective Results in individual cases were decisive and beneficial effects were demonstrated with regularity in all patients Bacteriologic findings with respect to disappearance of pneumococci from sputum were even more impressive than results of similar studies in patients treated with sulfonamides or penicillin Although penicillin was not used in any parallel and comparable cases in this study results may be considered entirely comparable to those observed in similar patients treated with adequate doses of penicillin Penicillin has the advantage of simplicity of administration generally lower toxicity and lower cost Aureomycin nevertheless may prove advantageous in cases of mixed etiology in penicillin sensi

(3) A k I t M d 84 857 874 Decemb 1949

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Aureomycin Treatment of Pneumococcic Pneumonia Clinical and Laboratory Studies on 33 Patients are reported by Thomas M Gocke Harvey S Collins and Maxwell Fin

(2) J Lab & Cl Med 35 15 219 Feb ry 1950

staphylococci from nose to skin Boils would seem to occur during the second stage of this process In support of this idea there is bacteriologic evidence that the skin is dependent on the nose for its staphylococcic contamination Further more the anatomic distribution of boils supports the idea of finger spread from some central depot The second stage not only is the stage of distribution onto the person s own skin but also may be the stage of distribution to the skin of other persons with or without the intermediate influence of towels etc

[The nasal cavity seems more dangerous than the oropharynx as a source of spread of hemolytic streptococcus as well as staphylococcus infection —Ed]

FRIEDLANDER PNEUMONIA

Clinical and Roentgen Manifestations of Pneumonia Due to Bacillus Mucosus Capsulatus (Primary Friedlander Pneu monia) are discussed by Max Ritvo and Francis Martin (Boston City Hosp) Friedlander pneumonia is a relatively infrequent severe disease with a high mortality approxi mately 70 80 per cent of cases terminating fatally As the incidence and mortality of ordinary types of pneumonia have been greatly reduced by modern methods of therapy the more virulent and resistant Friedlander pneumonia has be come of increasing importance It is now generally accepted that a small but definite percentage variously estimated at 0 5 5 per cent of all pneumonias are of the primary Fried lander type

Friedlander pneumonia is more common in males than in females the ratio being 5 1 Most patients are between age 40 and 65 Alcoholism often indicated by the history is prob ably a predisposing factor Malnutrition and other debilitating influences are also significant Onset is sudden usually start ing with cough sputum hemoptysis pleuritis pain and chill Cyanosis and dyspnea may be present Many patients appear desperately ill from onset of the disease Spt um may be brick red and homogeneous as though blood and mucus had been mixed to form an emulsion This appearance is found in only

(5) Am J Roe tg 1 6 211 22 A gu t 1949

tive patients and possibly in a rare case if there be such in which the causative pneumococcus is relatively resistant to penicillin

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STAPHYLOCOCCIC INFECTIONS

Boils Epidemiologic Survey is presented by G P B Whitwell and Ian Sutherland[4] (Inst of Social Medicine Oxford) In a previous survey of industrial surgery records kept by industrial nurses in a large factory employing a full time medical officer they found that there was a seasonal pattern for boils with a peak incidence during the fourth quarter and a minimal incidence in the first quarter of the year The peak incidence was unrelated to that for absence due to colds which occurs in the first quarter of the year

In the present study the authors investigated incidence of boils according to anatomic site Of a random sample of 500 lesions the majority occurred on the face head and neck Forearm and wrist were the next most frequently involved sites Boils in other sites were not common Study of the anatomic distribution of boils in each sex revealed an unexplained low proportion of neck boils in females (4 per cent) as compared with 26 per cent among males Despite traditional belief it is by no means certain how great a part is played by clothes friction in precipitating boils Of 37 consecutive neck boils only 3 were below the collar line In addition there were only 14 boils on the wrist an area where clothes friction is marked Of 37 workers with neck boils 12 had had a boil elsewhere or an infected hand sometime within the preceding six months Clipping the hairy skin may possibly in some way make it more vulnerable to invasion by staphylococci already present

These observations are in accord with the hypothesis that the skin is contaminated from the nose through the agency of fingers The hand which distributes staphylococcus from the nose may possibly be the agent by which these organisms reach the nose also If this theory is correct the hand has a twofold influence it contaminates the nose and it distributes

(4) Brit J Dermat 62 109 113 March 1950

DIPHTHERIA

Penicillin Treatment of Diphtheria Carriers is outlined by Samuel Karelitz and Vincent A Spinelli[6] (Willard Parker Hosp New York City) A Puerto Rican girl aged 7 had a typical fatal course of diphtheria She was a member of a family of 17 living in congested quarters Six members whose cultures and response to the Schick test were negative were not hospitalized Another member developed clinical symptoms and was hospitalized The other nine with positive cultures were admitted to a special ward and isolated from each other Eight had negative Schick test reactions and one a positive reaction The eight were observed daily without treatment for four to five days Cultures were made daily virulence type and penicillin sensitivity were checked

The patient with clinical symptoms and the positive reactor received 30 000 units of penicillin every three hours intramuscularly and nose drops of 1 cc penicillin in solution (1 000 units/cc) into each nostril every two hours during the waking day until five consecutive daily cultures were negative The former also received antitoxin

On the tenth hospital day all eight untreated carriers still had positive cultures Half the group were then given penicillin Cultures became negative within 36 hours and continued so After 21 days the untreated carriers were still yielding positive cultures Two of the four were given penicillin and had negative cultures within 36 hours Four days later one of the remaining two untreated carriers went on the penicillin regimen with similar results The carrier state of the last cleared spontaneously without treatment

Penicillin in the dosage indicated effectively eliminated Corynebacterium diphtheriae from seven carriers and one patient with faucial diphtheria in 36 hours One carrier required treatment for five days Thus penicillin effectively shortens the period of the carrier state of chronic diphtheria carriers

In six additional patients and one carrier a single intramuscular injection of 300 000 units of procaine penicillin in

(6) P d t 3 639 644 M y 1949

a small percentage of cases however the majority having sputum similar to that found in lobar pneumonia Bacteremia is common but is usually not pronounced and there is no direct relation between mortality rate and degree of bacteremia Acute Friedlander pneumonia usually ends in early death generally in two to six days Some patients recover rapidly and completely A third possibility is development of a chronic form of Friedlander pneumonia with necrosis and formation of one or more thin walled lung abscesses

Acute Friedlander pneumonia must be differentiated from pneumonia caused by the pneumococcus hemolytic streptococcus staphylococcus influenza bacillus and the viruses There is no single roentgen picture which occurs regularly in Friedlander pneumonia On the basis of a review of the literature and study of 14 personal cases the authors suggest the following roentgen classification of this disease

Massive lobar consolidation type (group 1) The affected portion of the lung is markedly and uniformly dense apparently due to large quantities of exudate At times a single lobe is involved or massive consolidation of the entire lung field may occur It is in this type that the roentgenologist may be of the greatest aid to the clinician

Lobular consolidation type (group 2) In early stages there is a patchy irregular density which later develops into a confluent consolidation scattered through one or more lobes

Chronic form characterized by lung abscess formation and pulmonary suppuration (group 3) These changes closely resemble pulmonary tuberculosis or bronchiectasis both clinically and roentgenologically

Streptomycin therapy appears beneficial in some cases of Friedlander pneumonia especially if commenced early in the acute phase Penicillin and sulfonamides do not appear to influence mortality

[Aureomycin chloramphenicol and terramycin should also be mentioned as therapeutic agents of possible value in Friedlander pneumonia An early presumptive diagnosis of this disease can be made from examination of a Gram stain of the sputum —Ed]

Serotherapy in Pertussis Edwin H Place Maurice J Keller and Ernest W Shaw[8] (Boston City Hosp) compared the effectiveness of three types of antiserums with each other Diagnosis of whooping cough was based primarily on clinical grounds and substantiated in most instances by the characteristic lymphocytic response or by positive nasopharyngeal cultures in questionable cases Of 150 consecutive patients with whooping cough 48 were untreated 38 received a refined horse hyperimmune serum 33 received a refined concentrated globulin fraction obtained from rabbit serum which had been immunized repeatedly with killed cultures of phase I Hemophilus pertussis and a pertussis endotoxoid and 31 received a concentrated globulin fraction prepared from human hyperimmune serum All treated patients were in the paroxysmal state of the disease At the beginning of the study single doses of 10 000 20 000 units of horse antipertussis serum were given intramuscularly When these appeared to be ineffective the dose was increased to as high as 75 000 units average dose for all patients being 40 000 units Most patients received the entire amount ir one injection the others received no more than two injections on consecutive or alternate days Similarly single doses of 10 000 units of rabbit antipertussis serum were given at first but were later scaled to as high as 75 000 units the combined average among all patients being 40 000 units In human hyperimmune antipertussis serum 2 5 cc is equivalent to 20 cc of the original serum Dosage varied from 2 5 to 10 cc (average 7 5 cc)

Any evaluation of a single therapeutic agent against whooping cough is extremely difficult because of the great natural variations in severity and duration of the disease There were no deaths in any of the four groups studied On the basis of day to day charting of paroxysms and vomiting weight changes and general appearance of patients no significant differences in the clinical courses of any of the groups were evident Significant reductions in absolute lymphocytosis

(8) J P d t. 34 699 710 J 1949

oil containing 2 per cent aluminum monostearate was given daily with appropriate doses of antitoxin Results indicated that large single daily doses will eradicate C diphtheriae All patients with diphtheria should be treated with antitoxin and penicillin preferably in large single doses of procaine penicillin in oil

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MENINGOCOCCIC INFECTIONS

Chronic Meningococcic Septicemia is described by Jørgen Piper[7] (Copenhagen County Hosp Gentofte Denmark) Chronic meningococcic septicemia occurs less frequently than chronic meningococcic bacteremia The disease has characteristic clinical features which even without bacteriologic examination make a fairly certain diagnosis possible Usually onset is acute often in connection with a catarrhal infection After this the course consists of similar attacks of fever every one to four days often periodically quite regular so that the temperature curve resembles that of tertiary or quaternary malaria Rash usually is macular or papular but sometimes resembles erythema nodosum Headache is a frequent symptom Nearly all patients complain of tenderness and pain in joints or muscles especially in lower extremities

In contrast to acute meningococcic sepsis the chronic form appears chiefly in younger adults and may be complicated by purulent meningitis endocarditis or epididymitis Meningitis may arise at any time in the course or chronic meningococcic septicemia may develop after an attack of meningitis Cerebrospinal fluid is normal unless the disease is complicated by meningitis Generally there is an increased number of white blood cells (up to 25 000) with relative neutrophilia Probably many patients have recovered from the disease at home without diagnosis ever having been made

[This syndrome is quite easily diagnosed clinically (1) fever (2) leukocytosis (3) pains in joints and muscles and (4) erythematous papular skin lesions especially about the knees and elbows It is seldom observed now because nearly everyone with fever of more than a few days duration is given antimicrobial therapy and meningococcic infections usually subside promptly with either penicillin or sulfonamide therapy —Ed]

(7) Acta m Scand 13 104 110 1950

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and good rises in serum agglutination titers followed serum therapy but these changes did not correlate with clinical improvement Though the number of both treated and control patients is small in view of the currently held ideas on the value of human hyperimmune serum therapy it is felt that this study suggests the need for further more critical and controlled evaluation of serum treatment of whooping cough Lack of fatalities though possibly influenced by serum is more likely the result of improved therapeutic procedures relating particularly to bacterial complications and to diligent nursing care

[This should about finish serotherapy for whooping cough. See the next two articles —Ed]

Aureomycin Treatment of Pertussis Shih Man Chang Edward Buist Wells Edwin H Place and Maxwell Finland[9] (Harvard Univ) report effects of aureomycin on clinical course and bacteriologic findings in 22 hospitalized patients compared with a similar number of comparable and contemporary patients treated on the same hospital ward without antibiotic therapy In all patients clinical findings were consistent with whooping cough and Hemophilus pertussis was identified in nasopharyngeal culture The two groups were comparable with respect to age distribution duration of symptoms at time of admission number and severity of paroxysms and occurrence of leukocytosis during the first days of hospitalization

Dosage of aureomycin used in the first 10 patients was 100 mg./kg body weight of crystalline hydrochloride daily for five days Subsequent patients were given 60 mg /kg daily for 10 days the period being prolonged because of inadequate bacteriologic and clinical responses in 3 of the first 10 patients Two of the three patients who relapsed were given a second course of aureomycin for five days Daily dosage was divided into four equal doses and given during feedings the contents of capsules being mixed with apple sauce or some other acceptable vehicle If vomiting occurred less than an hour after a dose the same dose was promptly repeated Antiserums were not used

Frequency and intensity of paroxysmal cough began to

(9) J Ped t 36 443 450 April 1950

decrease after the second or third day of aureomycin therapy and in most patients this decrease continued steadily until cough subsided completely and patients were discharged Average duration of paroxysmal cough was about 8½ days shorter among patients treated with aureomycin (21.7 days) than in those not so treated (30 3 days) For patients who re

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ceived aureomycin average number of paroxysms dropped sharply and steadily from the seventh to the fourteenth day leveled off for the next five days and then continued down ward more slowly (Fig 4) By contrast the first drop in average number of paroxysms among patients not given aureomycin occurred on the seventeenth hospital day and the decline then continued steadily Nasopharyngeal cultures be came negative for H pertussis soon after aureomycin was started and remained negative in all patients treated for 10 days Toxic effects from aureomycin were limited to mild

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(9) J Pediat. 36 443 450 April 1950

BRUCELLOSIS

Aureomycin Therapy in Human Brucellosis Due to Brucella Abortus In a previous study conducted in Mexico aureomycin produced more satisfactory immediate results than any other specific therapy in treatment of brucellosis due to Br melitensis These results were characterized by prompt clinical improvement sterilization of the blood and absence of serious side effects Abraham I Braude Wendell H Hall and Wesley W Spink (Minneapolis) treated successfully with aureomycin 16 patients in whom the infection was caused by Br abortus They describe the effect of aureomycin in these patients with bacteriologically proved brucellosis In most cases 2 Gm of the drug was administered daily in four divided doses at intervals of six hours Minimal treatment period was 10 days and the maximum 18 days

Clinical improvement was rapid and striking in all patients after treatment Bacteremia persisted after treatment in only one patient and a clinical relapse occurred in two others A comparison of aureomycin with a combination of streptomycin and sulfadiazine in two groups of 16 consecutive cases suggested that there is little difference in the over all results in infections due to Br abortus In certain respects however use of aureomycin is superior to combined use of the other two drugs Aureomycin produced almost immediate improvement in subjective well being in the patient and a rapid fall in temperature Oral administration is easy and free from dangerous side effects Hospitalization is not necessary Treatment with streptomycin and sulfadiazine has not been consistently attended by rapid improvement in symptoms or fever and the side reactions may be serious

Beneficial Effect of Chloromycetin® in Brucellosis is reported by Theodore L Woodward Joseph F Smadel William A Holbrook and William T Raby[3] Among gram negative organisms showing considerable sensitivity to chloromycetin® (chloramphenicol) in vitro and in vivo in animals are Brucella abortus Br melitensis and Br suis To test effec

(2) J A M A 141 831 835 N 19 1949
(3) J Cl In t gat 28 968 976 (pt 1) S pt mb 1949

vomiting and loose bowel movements in a few patients and did not necessitate discontinuing treatment The authors conclude that aureomycin appears to be beneficial in treatment of whooping cough

Pertussis Treated with Chloramphenicol Eugene H Payne (Detroit) Miguel Levy Gaston Moscoso Zamora Moises Sejas Vilarroel and Eduardo Zabalaga Canelas[1] (Cochabamba Bolivia) report on the treatment of whooping cough with chloramphenicol during a severe epidemic in Bolivia Because the supply of chloramphenicol was limited and the patients were many only those seriously ill were given the drug Diagnosis was confirmed by cough plate or swab cultures

Chloramphenicol was given in varying doses to 50 patients The drug was usually administered by mouth but in a few patients it was given as a rectal suppository or dissolved in propylene glycol and given intravenously Orally administered chloramphenicol was given in initial doses of 0 25 Gm to all but one patient who was given 0 50 Gm Children under age 6 months were given maintenance doses of 0 125 Gm three or four times daily children 6 months to 4 years were given 0 25 Gm three times daily children over 5 were given 0 25 Gm four times daily In addition chloramphenicol was administered intravenously to five children over 5 in initial doses of 0 30 Gm and maintenance doses of 0 30 Gm every three to five hours

Fever when present disappeared during the second day of treatment and paroxysms definitely decreased on the third day disappearing completely from the third to the sixth day However a light cough remained for several days possibly caused by residual inflammation in tissues Spot check by cough plate one week after treatment indicated that all patients were free from infection Untoward reactions to chloramphenicol appeared negligible In five children age 1 or less administration of the drug by rectal suppository in the same dosage as was used orally appeared as effective as oral administration

[Although whooping cough is a difficult disease in which to evaluate therapy these and other observations add up to fairly convincing evidence that we now have effective drugs for it —Ed.]

(1) J A M A 141 1298 1299 Dec 31 1949

lapse occurred but response to retreatment was prompt Only one patient had the more virulent melitensis type of brucello sis he responded favorably with return of temperature to normal in five days

It is not possible to decide from the limited evidence whether chloramphenicol or aureomycin is more effective in brucellosis Long term observation of a large series of pa tients varied treatment schedules and the possibility of toxic effects will need study before proper evaluation of these agents can be made in a disease so variable in its clinical man ifestations Until an optimal course of treatment is determined additional relapses may be expected it will be instructive to observe clinical effects after renewal of chloramphenicol therapy and to compare drug sensitivity of the organism causing the relapse with the one isolated during the initial attack It is probable that longer courses or perhaps periodic courses of antibiotic treatment may be necessary until a suf ficient degree of immunity develops

[The situation seems something like that in typhoid in that there is danger of relapse if therapy is discontinued after only a week or so —Ed.]

Treatment of Chronic Brucellosis with Chloramphenicol and Aureomycin is reported by Robert J Ralston (Holvoke Colo) and Eugene H Payne[4] (Detroit) Of 45 patients stud ied 18 were infected by exposure to cattle with Bang s disease or by drinking raw milk from infected herds Twenty had been similarly exposed but it was unknown whether or not infection was present in the animals and 7 had less definite histories

Duration of symptoms before treatment varied from a few weeks to six years most patients had had persistent symp toms for two years or more Complaints included in 42 fatigue and weakness in 35 various combinations of back ache joint and muscle pain in 22 irritability nervousness or insomnia in 17 severe mental depression in 16 gastroin testinal symptoms in 9 headache in 6 fever or sensation of warmth and in 3 symptoms simulating peptic ulcer Many other symptoms occurred less frequently One woman aged 28 complained of inability to become pregnant during a 30 month period following a normal gestation Two patients de scribed repeated attacks of fever chills weakness and malaise

(4) J A M A 142 159 161 Ja 21 1950

tiveness of this drug in patients with brucellosis an initial dose of approximately 50 mg/kg body weight was administered followed by 0 25 Gm every three hours until temperature was normal and then continued for a minimum of five

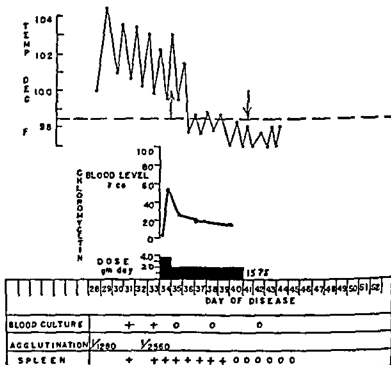


Fig 5—R s lts of bl mpb col t atm t i ma 27 w ght 160 lb w th bruc ll s of bort s type (Cou t y f Woodwa d T E t l J Cl I est gat on 28 968-976 (pt. I) Septembe 1949)

days Diagnosis of brucellosis was confirmed by blood culture before beginning treatment and by agglutination tests

Mean duration of fever before treatment in the nine patients studied was 30 days Two patients who were more seriously ill than the others improved within 36 hours after start of drug therapy and spent the most restful night since onset of illness Mean duration of fever for all patients after beginning *chloramphenicol* was *2 7 days* *Typical defervescence* after administration of the drug is shown in Figure 5 Symptoms abated shortly after beginning treatment One re

Although Hemophilus influenzae is a common cause of acute purulent meningitis in children this type of meningeal infection has rarely been encountered in adults Review of the literature reveals only 30 reports dealing with this disease in persons aged 20 or over The disease in the older age groups appears to differ in some respects from that in the very young as illustrated in the following case

Woman 48 was hospitalized with left anterior chest pain of two days duration Two weeks previously a severe upper respiratory infection associated with low grade fever and dry cough had developed. Fever subsided but cough persisted and with onset of chest pain it became productive of rusty sputum Four months before onset of the present illness diagnosis of the nephrotic stage of chronic glomerulonephritis had been made On a high protein low salt diet plus thyroid extract (1 gr three times daily) vitamin B complex and ammonium chloride she felt well and had only minimal edema of the legs Albuminuria persisted

Admission examination revealed an acutely ill woman with great respiratory distress Rectal temperature was 101 F pulse rate 100 and respiratory rate 32 There was splinting of the left thoracic cage. The percussion note was impaired over the left side of the chest posteriorly and in the left axilla Bronchial breathing was heard over the left lower lobe and there was a friction rub in the left axilla Fine moist inspiratory rales were present at the base of the left lung There was mild edema of both ankles Reflexes were normal A che t x ray and laboratory findings were consistent with a diagnosis of severe lobar pneumonia with the nephrotic syndrome

Despite penicillin therapy she became markedly stuporous and temperature rose to 103 2 F Penicillin dosage was increased to 200 000 units every three hours and two blood transfusions were given No meningeal signs were present until the evening of the third dav when she complained of severe headache and vomited Lumbar puncture then revealed cloudy cerebrospinal fluid containing 2,200 cells/cu. mm with predominance of polymorphonuclear leukocytes No organisms were seen on direct smear On the fourth day H influenzae type B was identified in the blood culture taken on admission and was also found in culture of sputum and cerebrospinal fluid Lumbar puncture was repeated and 100 mg streptomycin calcium chloride complex was injected intrathecally In addition 0 5 Gm streptomycin was given intramuscularly every six hours By the seventh day general improvement was clearly apparent The patient was discharged with no residual meningeal or pulmonary findings 24 days after admission

Most cases of H influenzae meningitis occur during the first three years of life It has been demonstrated that human blood is highly bactericidal for influenza bacilli and that the

for periods of two to five years they were asymptomatic in the intervals

Virtually no physical abnormalities could be found to explain the numerous and often disabling symptoms Temperatures were normal at the time of examination in most patients but a few showed elevations of 99 4 102 8 F No single diagnostic test was uniformly reliable Agglutination tests were positive in 10 patients skin reaction to brucella vaccine or to protein nucleate was positive in 37 improvement during treatment with brucellin antigen supported diagnosis in 26 of 28 patients

Forty patients were treated with 50 mg chloramphenicol/kg body weight in the first 4 12 hours followed by 0 5 Gm every 6 hours for 7 12 days they were observed for 3-8 months Partial to complete relief from symptoms was obtained in 35 Two of the five failures may be explained by erroneous diagnoses Three relapses occurred after the initial follow up period

Partial to complete relief was obtained in four patients treated with 2 5 3 5 Gm aureomycin hydrochloride daily for 10 days with maintenance of improvement through follow up periods of 3 9 months Inability of one patient to complete the course of treatment may explain the least satisfactory result Side effects were less troublesome from chloramphenicol than from aureomycin

Recently 22 more patients with chronic brucellosis were treated with chloramphenicol Thirteen reported favorable results and 2 unfavorable results were not available in the remaining 7

Of the total of 67 patients treated 5 relapsed A second course of 9 Gm chloramphenicol was given with definite response and alleviation of symptoms

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INFLUENZAL MENINGITIS

Influenzal Meningitis in Adults Report of Case Complicating Nephrotic Syndrome is made by Marvin C Becker and Clifford L Spingarn[5] (Mount Sinai Hosp New York City)

(5) Am J Med 7 269 273 Aug t 1949

sulfadiazine given in adequate dosage 120 000 units every three hours for three weeks intramuscularly and 40 000 units daily intrathecally for about seven days after the cerebro spinal fluid is sterile provides an effective remedy in treat ment of severe cases of influenzal meningitis The facts that streptomycin is not freely available and that the organism is known to develop resistance render streptomycin less gener ally useful

[Penicillin is probably not the drug of choice for influenzal meningitis The fact that it has any beneficial effect at all is surprising Before peni cillin was used clinically it was incorporated in bacteriologic culture mediums to suppress growth of gram positive organisms thus permitting i olation of H influenzae from throat cultures —Ed]

Hemophilus Influenzae Meningitis Observations on Treat ment of 110 Cases are reported by William G Crook B Reed Clanton and Horace L Hodes[7] (Baltimore) Cerebrospinal meningitis caused by H influenzae remains a formidable dis ease despite significant advances in treatment No single ther apeutic agent has proved successful in all cases Specific rab bit antiserum with sulfadiazine was the mainstay of treat ment in these cases until streptomycin became available

Of the 110 infants and children 79 per cent survived and 62 per cent recovered completely Of the 23 deaths 8 occurred within the first 24 hours after admission Slightly more than one half of the patients were under age 1 Of these only 69 per cent survived and only 50 per cent recovered completely compared with 90 per cent survival and 75 per cent with com plete recovery in the group over age 1 Forty four per cent were treated with specific H influenzae rabbit antiserum and sulfadiazine 48 per cent were treated with these agents and streptomycin the remaining 8 per cent were treated with streptomycin alone or in combination with sulfadiazine Sur vival and complete recovery rates of the first two group showed no significant differences The number of patients treated with streptomycin without serum was too small for analysis

In this series specific antiserum used early and in large doses was a valuable therapeutic agent It should be used in treatment of all patients except perhaps older children and younger ones who are only mildly ill High cost of this serum

(7) Ped t 4 643 659 Nov mbe 1949

bactericidal power is attributable to a humoral antibody Be tween ages of 2 months and 3 years this power is almost com pletely lacking from human blood but after age 3 it increases reaching its maximum in adults

Relationship of the nephrotic syndrome to onset of infec tion in this patient is of some interest since the former state may have impaired the immunologic defense of the patient In the nephrotic syndrome in children hypoproteinemia is associated with a definite decrease in the antistreptolysin titer Although there is no evidence available regarding the bacteri cidal power of the blood for influenza bacilli in adults with the nephrotic syndrome it is possible that this was reduced or absent as it is in infants The nephrotic state may there fore have been an important factor favoring onset of meningi tis at an age when the disease is uncommon

Penicillin in Treatment of Influenzal Meningitis Frances Braid and Richard B Meyer[6] (Childrens Hosp Birming ham) report their experience in treatment of 15 children with influenzal meningitis Of 11 treated with both sulfadiazine and penicillin 3 died 1 recovered but had permanent cerebral damage and 7 recovered completely One child died before more than one dose of penicillin had been given after only 24 hours illness Another who had been ill for eight days and was comatose on admission was given 40 000 units of peni cillin intrathecally daily for 12 days and 10 000 units intra muscularly every 3 hours for 36 days (an inadequate intra muscular dose) She died on the 36th day The third patient given one dose of 40 000 units of penicillin intrathecally and 50 000 units intramuscularly every 3 hours (also an inade quate intramuscular dose) died within 48 hours of admission The seven patients who recovered completely were given larger doses of penicillin

In three patients treatment was started with penicillin and sulfadiazine but penicillin was replaced by streptomycin on the second fourth and fifth days of therapy All recovered In none could it be said that penicillin had failed since it had not been given time to succeed One patient was treated suc cessfully with sulfadiazine and streptomycin

The authors conclude that penicillin combined with oral

(6) B M J 2 11 14 July 2 1949

zine were continued and in addition Alexander s specific rabbit anti influenzal serum was given After the fourth week when death seemed inevitable cerebrospinal fluid culture showed a relatively heavy growth of Hemophilus influenzae type B and cerebrospinal fluid glucose was zero polymyxin B was given For six days 7 mg (70 000 units) polymyxin B hydrochloride in 1 cc normal saline was given intramuscularly every four hours In addition 1 mg polymyxin was given intrathecally the first day and 3 5 mg the second and third days in 0 5 cc normal saline A remarkable recovery occurred

Such a recovery is highly significant because the prognosis of this disease present for four weeks in an infant aged 13 months with no detectable glucose in cerebrospinal fluid is poor with any therapy However there is one report of a patient aged 4 with meningitis due to H influenzae type B who recovered after five weeks following persistent therapy with specific rabbit anti influenzal serum and sulfadiazine

TULAREMIA

Aureomycin in Treatment of Tularemia Effectiveness of aureomycin therapy in brucellosis and rickettsioses suggested that it might also be useful in tularemia The drug exerts a bacteriostatic effect against Bacterium tularense in vitro and possesses striking suppressive power against tularemia in mice John C Ransmeier Harry J Price and Zerney B Barnes Jr[1] (Atlanta Ga) report results with aureomycin treatment of three patients with tularemia

Case 1—In man 37 presence of pneumonia associated with a history of rabbit contact suggested a diagnosis of tularemia though a lesion on the left thumb appeared purely traumatic and there was no peripheral lymphadenopathy Temperature ranged from 103 to 105 F without remission On the seventh day of illness aureomycin was begun in dose of 1 5 Gm orally every six hours for four doses then 1 Gm every six hours Within 24 hours temperature declined cough decreased and the patient was greatly improved Although he continued to feel well fever began to grow worse daily after five days aureomycin dosage was increased to 1 5 Gm every six hours but temperature continued to climb reaching 103 2 F two days later

(1) Am J M d 7 518 524 Octobe 1949

remains a major problem Streptomycin undoubtedly is a val uable therapeutic agent but in this study no striking improvement in over all results occurred after its introduction Sul fonamides especially sulfadiazine seemed to be of limited but definite value and their continued use in all patients is recom mended Penicillin in high dosage is also recommended as an adjunct to other agents

Aureomycin in Treatment of Influenzal Meningitis Miles E Drake J Edmund Bradley Jerome Imburg Fred R Mc Crumb Jr and Theodore E Woodward[8] (Univ of Mary land) report successful use of aureomycin in treatment of three patients with influenzal meningitis In general an initial intravenous dose of 100 mg aureomycin was followed by 50 mg every four or six hours Oral therapy was begun after 48 72 hours Total dosage per patient averaged 12 9 Gm given over an average of 11 8 days Regardless of degree of preced ing fever or age of the patient aureomycin therapy was fol lowed in each case by fall of temperature to normal within 96 hours of the initial dose By the third day of treatment abatement of such symptoms as mental dulness and convul sions was definite On the fifth day the acute phase of illness in all patients had completely disappeared The authors be lieve that aureomycin may represent a highly effective method of therapy in influenzal meningitis

Since this article was written the authors have treated four additional patients with influenzal meningitis successfully with aureomycin

[Here also serotherapy is going out because of development of effec tive chemotherapy —Ed]

Influenzal Meningitis Recovery of Case of Four Weeks Duration with Use of a New Drug, Polymyxin B (Aero sporin) B M Kagan[9] (Chicago) reports successful use of polymyxin B in an infant aged 13 months who had influenzal meningitis which failed to respond to streptomycin plus sul fadiazine and to delayed administration of specific rabbit anti influenzal serum Diagnosis was made early and streptomycin and sulfadiazine were given in large doses When progress was unsatisfactory after two weeks the infant was transferred to Michael Reese Hospital where streptomycin and sulfadia

(8) J A M A 142 463 465 Feb 18 1950
(9) Ped trics 4 319 3 Septembe 1949

sporing gram negative bacilli are classified in the genus Bacteroides These organisms are saprophytic inhabitants of the intestine urinary tract pharynx and female genital tract Comparatively few studies of infections induced by bacteroides have been reported in this country The impression prevails therefore that it is a rare cause of human disease

Bacteroides was recovered from 47 patients in Stanford University Hospital from 1940 to 1948 It was found to be a ubiquitous organism The female genital tract and various superficial areas of the body were the commonest sources It was encountered most frequently in young adults although all age groups were represented

Primary foci of bacteroides septicemia and bacteremia include tonsillar and peritonsillar abscesses similar lesions of the mouth and jaw otitis media purulent endometritis urinary tract infection and intestinal abscesses Many reported bacteroides septicemias might more accurately be designated as sepsis with bacteremia These septicemias and bacteremias are usually morbid processes with a high mortality rate Arthritis icterus pulmonary emboli and thrombophlebitis commonly occur with them Other writers have concluded that thrombophlebitis was the most characteristic finding Bacteroides infection of the central nervous system has been reported in 14 patients Meningitis was diagnosed in 12 Chronic otitis media was the common origin of such infection and invasion of the mastoid was rather common Bacteroides has been found with appendicitis peritonitis and infected carcinoma of the large intestine Only one of five patients with bacteroides peritonitis without bacteremia died whereas five of six patients with bacteroides septicemia from infected carcinoma of the bowel died

Bacteroides was isolated from purulent exudate in 11 of 13 patients with pulmonary infection (mainly putrid empyema) and pus recovered at operation yielded bacteroides in 14 of 16 cases of lung abscess Anaerobic diphtheroids and anaerobic nonhemolytic streptococci were found in all 16 specimens aerobic bacteria were isolated in only 3 instances Suppurative pulmonary emboli are reported to be common in bacteroides septicemia

Bacteroides is thought to be an important etiologic agent

The patient did not appear ill and cough had almost subsided Aureomycin was discontinued after a total dosage of 35 Gm Within 48 hours temperature was normal Agglutination test with Bact tularense antigen was negative on the 6th day of illness but became positive in dilutions of 1 2560 on the 16th day

CASE 2—Man 33 was hospitalized on the 14th day of a febrile illness On the left index finger there was a crusted ulcer and a firm tender node was palpable in the left axilla He had cut the finger and had been exposed to a rabbit During the first 48 hours in the hospital the fever followed a septic course Aureomycin was started orally in doses of 1 5 Gm every six hours and administered in smaller doses until the 23d day A total of 19 5 Gm was given Improvement was remarkable Within 12 hours of start of aureomycin temperature dropped to normal and symptoms subsided rapidly Serum agglutinins for Bact tularense were present in dilution of 1 640

CASE 3—Man 44 incurred an abrasion of the right index finger while hunting He killed and dressed five wild rabbits Three days later he had headache malaise and chilly sensations After three or four days pus drained from the finger lesion and a tender swelling appeared in the right axilla Diagnosis was ulceroglandular tularemia and aureomycin was started orally in dosage of 1 5 Gm every six hours for four doses after which dosage was reduced Within 24 hours the patient felt better and in 48 hours temperature was normal However temperature rose again a few days later and the axillary node became fluctuant The node was aspirated and temperature dropped immediately Agglutinins for Bact tularense reached a titer of 1 160 with no cross agglutination of Brucella abortus antigen

Although it is difficult to predict the course of tularemia without specific therapy in individual cases the authors believe that the first two patients were impressively benefited by aureomycin Aureomycin exerted no action on glandular suppuration in the third patient but streptomycin has also failed in similar cases These results encourage further trial of aureomycin in tularemia in man

[Chloramphenicol and terramycin are also effective Including streptomycin we now have four effective drugs for tularemia —Ed]

BACTEROIDES INFECTIONS

Clinical Significance of Bacteroides was studied by Paul M Beigelman and Lowell A Rantz [2] Certain anaerobic non

(2) Arch I t. Med. 84 605 631 Octobe 1949

(Memphis Tenn) believe that the incidence of infections and septicemia due to bacteroides is probably much greater than is reported These organisms are normal inhabitants of the mucous membranes and in case of injury to the mucosal sur faces may result in localized or widespread infections The 1939 edition of *Bergey s Manual of Determinative Bacteriology* classified the gram negative members of the anaerobic non spore forming bacilli under the genus Bacteroides In the past five years the authors have observed 18 cases of bacteroides infection They report two in which septicemia due to B funduliformis was treated with aureomycin hydrochloride

CASE 1—Negro woman 69 was hospitalized with a history of purulent nasal discharge cough headache sore throat chills fever nausea and vomiting of three weeks duration Temperature was 103 4 F pulse rate 105 respiratory rate 18 and blood pressure 180/120 The heart was enlarged and the abdomen distended and tympanitic The day after admission severe pain and tenderness developed in the right upper quadrant and the scleras became icteric The patient continued to have a septic fever and the liver became palpable

Two blood cultures for B funduliformis were positive Treat ment with penicillin sulfadiazine and streptomycin was ineffective Oral administration of aureomycin was impossible because of exist ing ileus Intramuscular aureomycin therapy was begun 11 days after admission The following dosage was used 750 mg in the first 24 hours 2 Gm in the second 24 hours 4 Gm in the third 24 hours and 5 Gm daily thereafter The septic fever disappeared on the fourth day of therapy In view of 10 negative blood cultures with clinical and physical evidence of improvement aureomycin therapy was discontinued after 75 45 Gm had been given

CASE 2—Negro woman 55 was hospitalized with a history of illness for three weeks Onset was marked by upper abdominal pain and vomiting Shortly after onset intermittent chill with high temperature elevation occurred A nonproductive cough was pres ent Physical findings were not remarkable except for a respiratory rate of 28 and moderate rigidity in the right upper abdominal quad rant and epigastric area

Shortly after admission the patient became icteric and the liver palpable and tender Despite massive doses of penicillin and strepto mycin with repeated blood transfusions the patient continued to have a septic fever with temperature spikes to 105 or 106 F daily Two positive blood cultures for Streptococcus faecalis and for B funduliformis were obtained At the height of the fever a third blood culture was positive for B funduliformis only Fifteen days after admission aureomycin therapy orally was instituted in the dosage given in Case 1 Response was dramatic The patient be

in chronic suppurative otitis media The organism has been isolated from the urine of four patients with urinary tract infection Pustular skin eruptions during bacteremic infection by bacteroides and cutaneous abscesses of the hand acquired by a person in contact with an animal infected by bacteroides have been described

Bacteroides is known to be a common saprophyte of the female genital tract It has been implicated mainly as a secondary invader in chronic and subacute pathologic processes of this system but its importance in puerperal fever has been indicated Severe and even fatal puerperal infection particularly following deliveries complicated by operative intervention has been attributed to bacteroides Bacteroides was the lone organism isolated in the authors series from most of seven circumscribed lesions of the female genital tract accompanying bacteria being present in only three

Treatment of bacteroides infection has included administration of potassium iodide vigorous aeration of local lesions administration of sulfonamide drugs streptomycin and penicillin surgical drainage and ligation of thrombosed veins particularly of the internal jugular vein in septicemia Definite value has been attributed to intensive treatment with sulfonamides in particular sulfapyridine although its beneficial effects have been irregular The organism may be penicillin resistant since seven of nine organisms tested displayed some degree of refractoriness to it

Gas formation by bacteroides in culture has been demonstrated and clinical evidence indicates that bacteroides infection must be considered in differential diagnosis of gas gangrene Consideration must also be given to the possibility of superimposed or concomitant infection by penicillin resistant bacteroides or other organisms complicating treatment of disease presumably caused by penicillin sensitive bacteria

[A good discussion of a type of infection which has too often gone unrecognized Sulfonamides have been effective in some cases others have responded to aureomycin as described in the next article —I d I

Septicemia Due to Bacteroides Aureomycin Hydrochloride Therapy in Two Cases Due to Bacteroides Funduliformis Leon V McVay Jr Frances Guthrie and Douglas H Sprunt[3]

(3) J A M A 140 1150 1152 Ag 6 1949

tents of 94 specimens of P americana Three pathogenic species were isolated Salmonella schottmulleri S oranienburg and S bredeney Organisms of doubtful pathogenicity recovered included Proteus vulgaris P morganii P mirabilis P rettgeri Paracolobactrum sp Alcaligenes faecalis and Pseudomonas aeruginosa Nonpathogenic organisms isolated included Escherichia and Aerobacter species and Eberthella oedematiens

Because of lack of conclusive evidence that roaches can transmit disease these insects have been regarded with tolerance by a large proportion of the population especially in areas where roach control is difficult The results cited suggest that such tolerance is unwarranted and that every effort should be made to suppress the cockroach and to protect food and kitchen utensils from contact with its feces Roach control is clearly of the highest importance in households that include infants

Since the authors study was completed other investigators have reported recovery of Salmonella bovis morbificans and Salmonella typhimurium from roaches captured in hospital wards in which cases of gastroenteritis due to S bovis morbificans were occurring

Treatment of Shigella Enteritis with Oral Streptomycin Report of 34 Cases In view of the toxic reactions observed with parenterally administered streptomycin Sidney Ross Frederic G Burke E Clarence Rice Harold Bischoff and John A Washington[5] (Washington D C) considered it worth while in 34 patients with enteritis caused by shigella organisms to use orally administered streptomycin exclusively Ages ranged from 3 months to 12 years Twenty five were admitted in the acute phase of the disease and 9 were carriers At least two positive cultures were obtained in each case before institution of therapy

During the initial phase of study 100-200 mg streptomycin was administered orally every four hours However it was soon found that larger doses were required to sterilize the bowel of its pathogenic organisms in active cases It was subsequently decided that 400 mg every four hours (2 4 Gm daily) was more efficacious and this latter dosage was used

(5) J A M A 141 183 185 Sept. 17 1949

came afebrile on the fifth day after institution of aureomycin therapy and remained so

Septicemia due to bacteroides especially the funduliformis type is exceedingly severe most cases terminating fatally Until the present there has been no specific or adequate therapy The excellent response to aureomycin hydrochloride in these two cases is therefore most encouraging

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ENTERIC INFECTIONS

Enteric Organisms from American Cockroach The significance of certain arthropods as vectors of disease has long been firmly established Though there have sometimes been good grounds for suspicion proof of the cockroach s definite part in disease *transmission* has been lacking Status of its role in disease transmission was summarized by Patton in 1930 as follows it is necessary to point out that although there is ample evidence that certain pathogenic organisms when fed to the cockroach can be recovered from its feces there is no proof that under natural conditions the cockroach becomes infected and then infects man s food Until pathogenic organisms have been recovered from the feces of cockroaches living under natural conditions and the findings confirmed by a bacteriologist the cockroach can like many other household insects be regarded only with suspicion

The investigation reported by Ruth S Bitter and O B Williams[4] (Univ of Texas) is concerned with search for members of the enteric group of bacteria present under natural conditions in the digestive tract of Periplaneta americana a roach which is readily available in Texas Material cultured consisted of contents of the hindgut obtained by dissection It seemed probable that bacteria isolated from hindgut contents would not differ significantly from those found in freshly deposited feces of the insect Results would therefore be an *index to type of contamination introduced into materials* soiled with roach feces

Cultures for enteric organisms were made of hindgut con

(4) J I fect D s 85 87 90 J ly A g. 1949

intestinal symptoms anorexia nausea vomiting abdominal pain and diarrhea were common All patients showed a brady cardia at onset a dicrotic pulse usually being present In 10 patients the spleen was palpable This was often not felt on admission but could usually be palpated toward the end of the first week Three patients had a tender palpable liver Rose spots were observed in only four patients three with typhoid and one with paratyphoid Blood cultures were positive in 10 patients 5 with typhoid and 5 with paratyphoid Stool cul tures of eight patients were positive six with typhoid and two with paratyphoid Agglutination studies showed no constant pattern Some of the more ill patients showed little or no rise in titer Others showed a significant increase followed by a fall whereas still others showed a sustained increase

Antimicrobial Therapy in Typhoid Vernon Knight Francisco Ruiz Sanchez Amado Ruiz Sanchez Selma Shultz and Walsh McDermott[7] investigated the use of antimicrobial therapy in 50 patients who were acutely ill with typhoid In four patients administration of polymyxin B did not result in beneficial effects definitely attributable to the drug and was accompanied with serious toxic manifestations In 31 of 34 patients given aureomycin uncomplicated recoveries oc curred and it was possible to show that duration of total ill ness was reduced in those who received treatment early How ever results were not uniform and frequently were negligible hence it is not possible to attribute them with certainty to the action of the drug

All 13 patients who received chloramphenicol recovered within approximately 72 hours regardless of severity or dura tion of infection when therapy was started This impressive superiority of chloramphenicol over aureomycin is virtually unique to typhoid it was not observed in a concurrent study of the two drugs in brucellosis and rickettsial infections

Relation of Relapses in Typhoid to Duration of Chloram phenicol Therapy is discussed by Joseph E Smadel Theodore E Woodward and Charles A Bailey[8] Early observations re vealed that relapses in typhoid were common in treated pa tients To eliminate such occurrences the authors prolonged

(7) A h I t M d 85 44 82 J ry 1950
(8) J A M A 141 1 9 S pt 10 1949

both in active and in carrier cases Duration of treatment ranged from 7 to 19 days Total dose varied from 8 4 to 57 6 Gm The drug was well tolerated and toxic reactions were not observed All patients including infants accepted the orally administered streptomycin well

Prompt disappearance of the pathogen from the stool followed initiation of streptomycin therapy in every case both in the acute and in the carrier group From daily stool cultures made during therapy it was found that the shigella organism disappeared from one to four days after start of treatment Clinically improvement was commensurate with the salutary effect observed bacteriologically In five patients a cultural reversal was observed on stool culture within one month after discharge from the hospital These reversals may have represented either a relapse or reinfection

For purposes of comparison 20 additional patients with bacillary dysentery were treated with sulfadiazine and 16 with aerosporin Results indicated that all three drugs are effective However in view of the toxicity of aerosporin streptomycin and sulfadiazine are considered preferable

Typhoid and Paratyphoid Fever in Immunized Subjects Arthur H Rosenblum[6] (Chicago) reports data on 17 cases of typhoid and paratyphoid fever occurring in immunized army personnel on Okinawa between August and November 1945 All patients were treated in a numbered general hospital on Okinawa There were eight cases of typhoid and six of para typhoid A fever In the other three cases laboratory confirmation was lacking but the courses were so similar to those in the confirmed cases that there was little doubt as to diagnoses All patients had a primary or stimulating injection of triple typhoid vaccine within a year

The typical clinical course was that of sudden onset with high fever repeated chills and anorexia In general symptomatology was similar in typhoid and paratyphoid A patients the former usually being more ill In all but one the disease was ushered in by marked hyperpyrexia usually temperatures of 104 106 F Only one patient with confirmed paratyphoid fever had the usually described steplike rise in temperature Of the 16 patients with chills 14 had recurrent chills Gastro

(6) An I t M d 31 235 44 A gu t 1949

were negative but in 5-40 days after termination of therapy cultures once again became positive for salmonella It is difficult to explain these disappointing results Before therapy chloramphenicol sensitivities of the various salmonella strains ranged from 2 to 5 μg/cu cm which places the organism among the relatively sensitive group of bacteria susceptible to the drug and no increase in chloramphenicol resistance was observed after bacteriologic relapse

All patients recovered clinically with rather prompt cessation of diarrhea and general improvement in nutritional status The part played by chloramphenicol in clinical improvement is difficult to assess in view of the fact that many untreated cases of salmonella enteritis managed with adequate supportive measures run a mild self limiting course provided no complications supervene

[These results are disappointing in view of the apparent similarity of the typhoid bacillus to other salmonellas —Ed]

TUBERCULOSIS

Concentrated Roentgen Therapy of Cervical Tuberculous Lymphadenitis Introduction of streptomycin as treatment for tuberculous involvement in various parts of the body raises the question as to present status of roentgen treatment of tuberculous adenopathy Purposes of this report by Isadore Lampe Clarence P Chrest and Donald A Koch[1] (Univ of Michigan) are to re emphasize the high quality of results obtained by roentgen therapy to point out advantages in time and convenience of their particular plan of treatment and to contrast results of roentgen therapy with streptomycin in treatment of tuberculous adenopathy

During 1939 47 42 patients with cervical tuberculous lymphadenitis received roentgen therapy Among these treatment was completed and follow up was considered adequate in 37 and these form the basis of the study Diagnosis was confirmed by pathologic or bacteriologic material in 30 cases The remaining seven patients presented clinically characteristic features of tuberculous adenopathy three having radio

(1) Am J M S 217 632 636 J n 1949

the course of treatment in persons infected with Salmonella typhosa Analysis of results in 44 patients with typhoid given chloramphenicol therapeutically indicated a striking relation between duration of chemotherapy and incidence of relapses The initial loading dose was 3 4 Gm chloramphenicol given orally followed by 1 3 Gm daily in divided doses for variable periods Clinical relapse with reappearance of bacteremia occurred in 7 of 13 patients whose initial course of drug was given for eight days or less No relapses occurred among 19 patients treated for 9 14 days or among 12 treated for 14 23 days The authors conclude that chloramphenicol should be given in adequate amounts for more than eight days to patients acutely ill with typhoid if relapses are to be avoided There appears to be little advantage in continuing treatment for more than 14 days

Chloromycetin® in Treatment of Salmonella Enteritis Salmonella infections have shown a singular refractoriness to chemotherapeutic and antibiotic agents Successful use of chloramphenicol (chloromycetin®) in typhoid fever suggested that it might be effective in salmonella infections During the past five months Sidney Ross Frederic G Burke E Clarence Rice John A Washington and Sara Stevens[9] (Washington D C) used chloramphenicol in treatment of nine infants with salmonella infections In all nine infection appeared to be limited to the gastrointestinal tract In every case the chief complaint on admission was diarrhea of 3 11 days duration

The dose of chloramphenicol was 0 75 3 0 Gm daily in a four hour divided dosage schedule for an interval of 9 18 days To administer the drug orally in this infant group it was necessary to empty out contents of the capsule and administer it in different palatable vehicles in an effort to disguise the taste These included sirup of yerba santa chocolate milk chocolate sirup cherry sirup and applesauce A mixture of chloramphenicol and sirup of yerba santa followed by chocolate milk was perhaps the least offensive method

Results were not singularly gratifying Of the nine patients treated only two showed continued negative stool cultures after four months follow up In the other seven patients there was a transitory period in which stool cultures

(9) N w E gland J Med 242 173 176 F b 2 1950

were negative but in 5-40 days after termination of therapy cultures once again became positive for salmonella. It is difficult to explain these disappointing results. Before therapy chloramphenicol sensitivities of the various salmonella strains ranged from 2 to 5 μg./cu. cm., which places the organism among the relatively sensitive group of bacteria susceptible to the drug, and no increase in chloramphenicol resistance was observed after bacteriologic relapse.

All patients recovered clinically with rather prompt cessation of diarrhea and general improvement in nutritional status. The part played by chloramphenicol in clinical improvement is difficult to assess in view of the fact that many untreated cases of salmonella enteritis managed with adequate supportive measures run a mild self limiting course provided no complications supervene.

[These results are disappointing in view of the apparent similarity of the typhoid bacillus to other salmonellas.—Ed.]

TUBERCULOSIS

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During 1939-47, 42 patients with cervical tuberculous lymphadenitis received roentgen therapy. Among these treatment was completed and follow up was considered adequate in 37 and these form the basis of the study. Diagnosis was confirmed by pathologic or bacteriologic material in 30 cases. The remaining seven patients presented clinically characteristic features of tuberculous adenopathy, three having radio

(1) Am. J. M. S. 217:632-636, June, 1949.

graphic evidence of active or quiescent pulmonary tuberculosis and one having calcium in cervical nodes

TECHNIC—Radiation was generated at 200 kv filtered with 0 5 mm Cu and 1 0 mm Al (half value layer 0 9 mg Cu) at a target skin distance of 50 cm and at a rate of about 50 r/min Fields were large enough to include the obviously diseased nodes as well as the regional group and varied from 8 × 10 cm to 15 × 15 cm. Treatment was given daily 200 r (measured in air) to one field for four or five days In children or debilitated adults 100 150 r to one field was given Usually total dosage was 800 1 000 r/field and at completion the patient was asked to return in two to three months Occasionally a patient was given a second course at that time If good regression did not follow the second course response was considered unsatisfactory and further radiation was not given

Reactions ensuing from this method were insignificant Regression was complete in 31 patients 6 showed unsatisfactory response Of the 31 showing complete regression 23 had draining sinuses at inception of therapy some of these sinuses having developed after biopsy or drainage of fluctuant masses Of the six patients whose response was unsatisfactory four had draining sinuses It therefore appears that draining sinuses have no particularly adverse effect on results of radiation therapy Conservative surgical procedures are advantageously combined with irradiation Fluctuant masses on the verge of breakdown may be aspirated or incised for diagnostic or therapeutic reasons Radical neck node dissections should play no part in modern management of tuberculous adenopathy and can usually be avoided

Review of recent literature reveals a favorable comparison of results obtained by this treatment with the best results obtained elsewhere To contrast roentgen therapy results with those of streptomycin in treatment of tuberculous adenopathy recent reports of the Council on Pharmacy and Chemistry American Medical Association were studied Report of the Sub Committee on Streptomycin contains the following statement For the present streptomycin should not be used in the treatment of minimal pulmonary tuberculosis or other lesions that may be expected to clear on older and accepted forms of therapy Results of treatment with radiation lend additional support to the belief that streptomycin therapy might best be reserved for the 15 20 per cent of cases which are resistant to adequate treatment by roentgen therapy

[Something to be kept in mind We are likely to forget the possibility of roentgen therapy while debating the choice of chemotherapy surgery or rest only—Ed]

Tuberculous Peritonitis Treated with Streptomycin Ruth H Wichelhausen and Thomas McP Brown[2] (Veterans Admin Hosp Washington D C) report the response of tuberculous peritonitis to streptomycin therapy in 26 patients in various Veterans Administration hospitals Symptoms and clinical observations in these patients were the same as those reported elsewhere Most patients had fever and in many it had been present for many weeks or months Onset of abdominal symptoms was acute in 9 patients and insidious in 10 In seven patients there was a tendency to recurrent episodes Abdominal pain and swelling nausea vomiting and anorexia were consistent complaints Cough was a complaint of 10 patients in 6 it could be attributed to coexisting pulmonary or pleural involvement Shortness of breath was a complaint of seven patients This was explained in two patients by accumulation of ascitic fluid resulting in increased subdiaphragmatic pressure Because joint pain was the initial symptom one patient was diagnosed as rheumatic heart disease and treated as such for almost one year before diagnosis of tuberculous peritonitis was established Abdominal distention varied from moderate to severe in these patients In several patients in whom ascites had been present at some time fluid was not found at laparotomy It appeared that accumulation of ascitic fluid had ceased spontaneously and the fibrinous or gelatinous exudate found instead represented the intermittent stage between free fluid and adhesions Four patients presented the clinical picture of intestinal obstruction

In seven of eight patients barium enemas were unrevealing in one case there was evidence of a mass encroaching on the sigmoid and cecum In 12 of 16 cases gastrointestinal series revealed no abnormalities Laparotomies in 20 patients and peritoneoscopy in 2 others revealed gross evidence of tuberculous peritonitis in 21 Histopathologic diagnosis of tuberculosis was made in 20 cases and in 9 caseation necrosis was noted In only five cases was the histologic diagnosis substantiated by demonstration of acid fast organisms

The extraperitoneal tuberculous manifestations in these

(2) Am J M d 8 421 443 April 1950

patients were miliary, pulmonary and genitourinary tuberculosis pleural effusion pericarditis adenitis draining sinus and abscess Only 5 of the 26 patients never showed tuberculous involvement other than peritoneal Routine laboratory studies contributed little to diagnosis though absence of leukocytosis was characteristic In this series of 26 cases 26 different admission and differential diagnoses were advanced Many diagnoses were quickly discarded However, review of these records from 22 different hospitals showed that certain diagnoses were frequently made by different observers Many patients presented the picture of an acute abdomen due to cholecystitis acute appendicitis ruptured appendix pelvic abscess or a perforated ulcer necessitating surgery It is easily conceivable that dense adhesions may lead to intestinal obstruction Amebic abscess of the liver was an important diagnostic consideration in two patients who were subjected to extensive studies before diagnosis of tuberculous peritonitis was made by exploratory laparotomy

All patients in whom diagnosis of tuberculous peritonitis had been made were given streptomycin as soon as it was available Daily dosage was 1 3 Gm intramuscularly in two to six divided doses Total dosage per patient varied from 42 to 254 Gm for a single course Duration of therapy was 21 137 days One of the most striking and dramatic responses to streptomycin was subsidence of fever Fever was present in 21 patients when streptomycin therapy was initiated and 18 became afebrile during or shortly after therapy Abdominal pain tenderness rigidity swelling and distention receded more gradually but most patients were much relieved after one to two weeks In 10 of 11 patients ascites disappeared in the first two to four weeks of therapy Failure to reaccumulate ascitic fluid and rapidity with which it was absorbed were remarkable in several patients Six patients presented the complication of a draining sinus of the abdominal wall All sinuses closed under streptomycin therapy including a sinus in a fatal case in which there was no other response to streptomycin Nausea vomiting diarrhea and constipation were present in only 3 of the 24 surviving patients at completion of therapy Concensus of all observers was unanimous concerning striking general improvement as evidenced by a

feeling of well being improved appetite and gain of weight and strength

Four patients relapsed after initial improvement One died The three other patients were given a second course of streptomycin to which two responded favorably and one re mained unchanged Follow up observations were possible in 23 of the 26 patients There were two deaths The remaining 21 patients had been observed for 2 29 months at the time of this report Whereas these patients appeared to have recov ered from tuberculous peritonitis extraperitoneal tuberculo sis was not controlled in eight It was noteworthy that pa tients who received 1 Gm streptomycin daily improved as satisfactorily as those treated with larger daily doses

Streptomycin in Development of Hydrocephalus in Tuber culous Meningitis Since the introduction of streptomycin in treatment of tuberculous meningitis several reports of hydro cephalus have appeared One report cited 46 instances of hydrocephalus found at 53 necropsies of patients with tuber culous meningitis treated with streptomycin by various routes These reports led S N De[3] (Univ College Hosp Med School) to investigate histologic changes in the basal men inges from eight patients with tuberculous meningitis to de termine if administration of streptomycin modifies the lesion in any way that might lead to hydrocephalus Six were hydro cephalic and two were not Seven had been treated with strep tomycin intramuscularly and intrathecally with or without streptomycin intraventricularly for 12 231 days Only one patient (hydrocephalic) received no antibiotic treatment

The basal subarachnoid space in all the hydrocephalic patients was completely blocked by a fibrinous exudate and thick tuberculous granulation tissue Two of the five treated patients showed some fibroblastic proliferation in the exudate mainly directed against the fibrinous elements but also partly encircling some minute tubercles The other three showed no evidence of organization nor was there any obvious histologic modification of the lesions by streptomycin when compared with lesions in the untreated patient

Fibrosis of tuberculous lesions is known to be a general response to streptomycin treatment Suspicion was naturally

(3) B t M J 2 214 216 J ly 23 1949

aroused that streptomycin in the course of promoting healing of tuberculous lesions in the meninges might lead to fibrosis and adhesions resulting in obstruction of the circulation of cerebrospinal fluid and consequent hydrocephalus The fact that streptomycin had been given intrathecally in many reported cases of hydrocephalus strengthened the view that leptomeningeal adhesions after such treatment were responsible for the blockage However in the present investigation only two of the five streptomycin treated patients showed some fibroplastic proliferation in the basal leptomeninges although this reaction did surround a few tubercles it seemed to be mainly directed along the fibrin threads in the exudate In addition some degree of organization and repair in meningeal lesions in the more protracted cases was noted in pre streptomycin days Long ago scar tissue was recorded as replacing antecedent tuberculous lesions in the meninges in patients who had recovered from tuberculous meningitis a tendency to fibrosis of meningeal exudate was also pointed out These facts suggest that formation of leptomeningeal adhesions has not always been responsible for the observed hydrocephalus nor has it been especially brought about by treatment with streptomycin

A search through the older literature suggested that tuberculous meningitis by itself has long been suspected of being associated with hydrocephalus The author concludes that tuberculous meningitis can give rise to an internal hydrocephalus associated with complete blockage of the cisterna pontis by tuberculous granulation tissue and a copious fibrinous exudate but independent of the development of cisternal fibrosis There is no convincing evidence that streptomycin increases the chance of this complication by stimulating production of reparative tissue The prominence given to the condition since introduction of streptomycin probably results from more careful examination of the brain in such cases

[The apparent increased incidence of hydrocephalus could well be due to longer survival under streptomycin therapy permitting the hydrocephalus to become obvious —Ed]

MYCOTIC INFECTIONS

Immunologic Types of Blastomycosis Report on 40 Cases is presented by David T Smith[4] (Durham N C) Durham is near the center of the southeastern endemic area of blastomycosis and over 50 cases have been studied in Duke University clinic in the past 18 years Approximately 45 per cent of the infections were confined to the skin 45 per cent invaded internal organs and 10 per cent involved both skin and internal organs

Prognosis seems to depend at least in part on the patient s immunologic status Some patients develop humoral antibodies which can be detected by the complement fixation test and others acquire a hypersensitivity to the antigen of the organism as shown by a positive skin test either to a vaccine or to blastomycin

In Smith s series of 40 patients the 10 with positive skin tests without complement fixing antibodies had the best prognosis Previous experience revealed that patients with positive skin tests to a blastomyces vaccine either did not improve or actually became rapidly worse when iodides were administered Therefore Smith made it a practice to produce partial desensitization with a blastomyces vaccine before giving iodides or treating local lesions with x rays

In general the 10 patients with positive skin tests and positive complement fixation had more extensive infections than those with positive skin tests alone Treatment was similar namely desensitization followed by iodide therapy

In 10 patients skin tests were negative but complement fixing antibodies were present in titers ranging from 1 4 to 1 64 All these patients had extensive generalized disease and all but two were obviously critically ill when first seen A negative skin test is interpreted as the result of a terminal anergy analogous to that seen in patients dying of generalized tuberculosis Death of 8 of the 10 patients with negative skin tests and high titers of complement fixing antibodies is analogous to results reported for cases of coccidioidomycosis

(4) A Int. Med 31 463 469 S pt mb 1949

An immunologic response consisting of a negative skin test and negative complement fixation occurred in one terminal case though usually high titer of complement fixing antibodies is present in terminal cases Nine other patients with a negative skin test and negative complement fixation apparently had recent infections and had not yet had time to develop either hypersensitivity of the skin or complement fixing antibodies

Smith concludes that prognosis is best in blastomycosis patients with positive skin tests and no demonstrable antibodies in the serum and poorest in those with negative skin tests and a high titer of complement fixing antibodies in the serum Patients with positive skin tests should be desensitized before being treated with iodides regardless of presence or absence of antibodies Patients with neither positive skin tests nor complement fixing antibodies should be actively immunized with a heat killed vaccine made from the yeast phase of B dermatitidis before being treated with iodides

[This represents an unusually large number of cases to be observed in one clinic The author appears justified in separating them into groups on the basis of immunologic tests—Ed]

Visceral Actinomycosis V Zachary Cope[5] points out that the only actinomyces which commonly gives rise to this disease in man is A bovis which only grows when oxygen is excluded or present in minimal amount This common pathologic agent which is responsible for nearly all lesions in man has never been found outside an animal body It has never been found on grasses grains hay or straw and the farm hand is not more likely to become infected than the city clerk In man it often lies latent in the carious crevices of teeth or in deep crypts of the tonsils It occurs with equal frequency in all economic classes but it is more common in men than in women

That this organism which is so frequently present in the body does not cause disease more often is due to the fact that it is difficult for it to penetrate normal epithelial surfaces When by accident disease or necessary operation the epithelial surface is broken actinomyces may escape into cellular tissues and begin to grow well away from the surface The

(5) A n R y Coll Surgeo s Engla d 5 394-410 Dec mber 1949

tissue reaction is rarely acute it may form an abscess in which the fungus grows plentifully but not in the form of granules More commonly the reaction leads to formation of a mass of hard fibrous tissue which is almost avascular and on section looks like a sarcoma or scirrhus carcinoma Sometimes small abscesses may be seen embedded in this tissue but in many cases careful microscopic examination is necessary to find *any trace of the organism Sooner or later softening oc curs and an abscess is formed in which granules are present* It is difficult to escape the conclusion that the dense fibrous reaction of the mesenchymal cells results from some degenera tive or secretory product of the organism itself Actinomyces can remain latent in tissues for months or years because of their ability to maintain existence in avascular tissue and be cause of the protective arrangement of the fungus in tissues—growing hyphae surrounded by a palisade of clubs

It is now thought improbable that infection results from grass or straw The carious tooth is thought to be the usual source When the fungus is in the mouth it is inevitable that from time to time portions will be swallowed and pass through the alimentary canal In most cases no harm results but in areas in which fungus may contact an ulcerated surface or when inflammatory processes give it an opportunity to extend it may cause serious disorders If fungus reaches the perito neal cavity it may cause a subphrenic abscess may invade the liver or may gravitate to the pelvis and form a tumor After perforation of the appendix the lesion may extend by con tiguity down into the pelvis into the psoas muscle toward the kidney and to the vertebral column Thoracic infections are also due to spread of infection from the mouth The wonder is that pulmonary actinomycosis is comparatively rare for the microbe is so often present It is the rule for pulmonary actinomycosis to invade the thoracic wall and come to the sur face unlike tuberculosis The thorax sometimes becomes in fected through the bursting of an hepatic abscess through the diaphragm or it may become involved by a low cervical infec tion descending into the superior mediastinum The vertebral column is affected in a way quite different from that with any other infection The process commonly affects the bodies and transverse processes but it may invade any part with which

it comes in contact There is a slow process of absorption and simultaneous formation of new bone which maintains the framework and strength of the bodies so that collapse of a vertebra is rarely seen

In the abdomen there is usually a hard swelling which is significant when it forms around the sinus left by drainage of an appendicular abscess When such a tumor develops in the pelvis or around the colon without any warning it is usually mistaken for a malignant growth When actinomycosis attacks the thorax it may closely simulate tuberculosis pneumonitis pleural effusion empyema or malignant growth when it invades the mediastinum it may look like a mass of glands when the vertebrae are involved it may simulate osteomyelitis or give rise to meningeal symptoms Actinomycosis might well be called the most misdiagnosed disease' Agglutination complement fixation estimation of opsonic index precipitin test and a cutaneous reaction have all been found unreliable

Much of the treatment for actinomycosis advocated in books is obsolete Penicillin is the most effective treatment At first short courses of comparatively small doses were given improvement occurred but did not prove lasting so repeated courses were required Later when doses were bigger results were better and cure was sometimes attained Often however recurrence took place after some months It then became evident that for severe cases of visceral actinomycosis it was necessary to give large doses of penicillin for long periods There should be no intermission until the patient has been symptom free for weeks or months If response to penicillin is slow or absent there may be some advantage in combining it with one of the sulpha drugs Abscesses must be opened or if small aspirated With a massive lesion of the stomach intestine or kidney excision of the affected part may be necessary But now it is never needful to excise portions of lung or even to remove those masses of fibrous tissue which develop in this disease

Actinomyces Bovis in Tissues and Body Fluids Philip Schain Anne De Stefano and Joseph P Kazlowski[6] (Veterans Admin Hosp Staten Island N Y) report the inci

(6) J Lab & Cl Med 34 677 679 M y 1949

dental finding of A bovis in diseases other than actinomycosis The study was prompted by discovery of A bovis in bone marrow aspirated from a patient suspected of having brucellosis but later found to have Hodgkin s disease Consequently various materials such as blood and bone marrow from all subsequent patients with Hodgkin s disease brucellosis or related syndromes were cultured for this organism

A bovis in pure culture was isolated from the body fluids and tissues of four patients with proved Hodgkin s disease from one with a disease associated with brucellosis from one diagnosed clinically as having abdominal granuloma and from one with xanthoma tuberosum A bovis was not found in the single bone marrow samples from two patients with proved Hodgkin s disease and from six patients with blood dyscrasias or from over 1 000 blood samples and approximately 7 500 other specimens grown in the same fashion

This article is published solely to present the incidental finding of A bovis in diseases other than actinomycosis The authors do not intend to indicate that A bovis is the causative agent of any disease other than actinomycosis Finding of this organism in tissues and body fluids of patients with granulomatous diseases is provocative It is entirely possible that if other disease entities are investigated similar observations might be made

VIRAL RESPIRATORY INFECTIONS

Modern Viewpoint on Influenza is presented by C H Stuart Harris[7] (Univ of Sheffield) The virus etiology of influenza and existence of two major groups of viruses A and B are now accepted Existence of minor antigenic variants explains description of the viruses as groups rather than types Significance of the fact that virus particles exist both as small globoid structures and as long threadlike filaments is unknown

In countries where an attempt has been made to follow influenza epidemics over a number of years a definite periodicity was noted Influenza A epidemics occurred more com

(7) P act t one 163 481 487 D cembe 1949

monly every two or three years than every year influenza B epidemics occurred every four to six years

Clinical descriptions of the influenza in the epidemic of June 1918 are similar to observations made in recent epidemics of mild influenza Mild influenza is characterized by a three day fever accompanied by headache muscular pains shivering and cough Influenza is recognized not so much because of its severity but because of suddenness of onset pyrexia and absence of localizing signs except for those in the throat or chest A diagnosis of influenza is also suggested by illness in other members of the family Pulmonary complications vary greatly in incidence In many rales or rhonchi may be elicited by repeated examination but signs of actual consolidation occur in only a minority The commonest complications are probably bronchitis or bronchiolitis in which cyanosis is relatively prominent compared with pyrexia or cough

True influenzal pneumonias are not common occurring primarily in persons over 45 In persons over 65 influenzal pneumonia often causes death It begins with the ordinary symptoms of influenza followed by sudden onset of dyspnea and cyanosis There is little chest pain and cough may be less prominent than dyspnea The sputum may contain many organisms Staphylococcus aureus is often found The disease usually lasts for several days but changes in severity can occur rapidly Response to treatment is poor

The two characteristics which distinguish influenza from colds catarrhs pharyngitis bronchitis or atypical pneumonia are (1) the presence of influenza virus in the throat and nose during early stages (2) the increase in antibodies with specific virus neutralizing or complement fixing properties which are directed against the virus antigens present during convalescence The presence of the virus or antibodies can be determined by inoculating fertile hens' eggs or ferrets with the patient s sputum or by serologic studies

Immunity to influenza is imperfectly understood It is known that natural immunity is at its peak soon after an attack and is temporary Protective antibodies must be an important factor in defense however of two persons with the same antibody level before an epidemic only one may become infected Attempts to find the basis of a nasal factor in defense

have not been successful although it is apparent that nasal epithelium in some persons is better able to protect itself than that in others Artificial immunization has serious limitations vaccines are slow acting and maximal effectiveness is not reached until two to four weeks after injection Because it is difficult to know when to expect an epidemic and because infection spreads rapidly the correct timing of immunization is a major problem Another obstacle is the determination of the most suitable virus vaccine The most potent vaccine gives the best antibody response but it also induces the most severe reactions Such reactions are of the general character seen after the injection of triple vaccine and are sufficiently unpleasant to limit the size of the dose They appear to be due to the virus rather than to impurities Because children react more severely than adults the dose must be smaller than is desirable in view of their less prepared defense mechanism Multivalent vaccine is used because the antigen appropriate to the virus strain likely to be the cause of the forthcoming epidemic must be given However it is possible that variants exist which are unknown and not in available vaccines

It is doubtful if the mild influenza of recent years is more to be dreaded than a campaign of mass immunization Mass use of a vaccine which is only temporarily effective is not practical However an effective vaccine would be of great aid if an epidemic similar to the one in 1918 occurred

Antihistaminic Drugs in Therapy of Common Cold In view of the unusually satisfactory results he obtained with benadryl® in treatment of the common cold John M Brewster[8] (U S Naval Hosp Great Lakes Ill) attempted to find whether other antihistaminic drugs would be as satisfactory

Clinics or stations for treatment of colds were established at three focal points on the compound All personnel were encouraged to report for treatment at the earliest possible moment after onset of a cold Pyribenzamine® thenylene® neo antergan® and histadyl® as well as benadryl® were the drugs used Codeine sulfate combined with papaverine hydrochloride was used as control medication An effort was made to give the various drugs to patients in succession and without selection Thus approximately every sixth patient re

(8) U S N M B ll 49 1 11 Ja F b 1949

ceived control medication and an equal number received one of the five drugs To combat the sedative effect of antihistaminic drugs racemic amphetamine sulfate (benzedrine®) in 2 5 5 mg doses or dextroamphetamine sulfate (dexedrine®) in 5 10 mg doses was frequently given with the initial dose of anti histaminic drugs whenever treatment was begun before 4 p m These effectively reduced the sensation of drowsiness in most cases and had the happy effect of lifting many patients out of the mild mental depression that is often a symptom of colds

The dosage for adults was arbitrarily set at 50 mg for antihistaminic drugs and at 16 mg each for codeine sulfate and papaverine hydrochloride

A total of 572 patients were treated from October 1947 to May 1948 A cold was considered aborted or cured when all signs and symptoms disappeared within 24 hours of beginning treatment and remained absent for at least 48 hours after all treatment was stopped

All symptoms were aborted in 19 (90 per cent) of 21 patients given antihistaminic drugs within the first hour after onset of symptoms and in 48 (87 per cent) of 55 patients treated within two hours of onset Of 156 patients who received treatment within 6 hours 116 (74 per cent) were cured as were 165 (70 per cent) of 234 patients given treatment within 12 hours

Seventy seven patients were used as controls Within one hour after onset of symptoms cure was obtained in one of two patients to whom control medication was given Cure was obtained in 5 (42 per cent) of 12 patients who received control medication within 6 hours and in 7 (31 per cent) of 22 treated within 12 hours In none in whom therapy was begun more than 24 hours after onset was cure obtained

Brewster concludes that two or three doses of these anti histaminic drugs at four hour intervals are adequate to effect abortion of symptoms of colds in 90 per cent of patients given treatment within a few hours after onset

The phenomenal cure of very early colds by use of anti histaminic drugs seems to justify the assumption that the common cold begins as an allergic reaction

[This is the report that set off all the furor resulting in the use of millions of antihistaminic pills by cold sufferers It is disposed of in part by the American Medical Association s report which follows Other

studies in which placebos were alternated with antihistamines and in which neither clinician nor patient knew which was being used have shown no benefit whatever from antihistaminic therapy —Ed]

Status Report on Antihistaminic Agents in Prophylaxis and Treatment of Common "Cold ' is presented by the Council on Pharmacy and Chemistry of the American Medical Asso ciation[9] The barrage of publicity in the lay press radio an nouncements advertisements and pharmaceutical brochures is based almost entirely on the work of Brewster and of Ar minio and Sweet In none of these or of other studies was diagnosis established beyond reasonable doubt and in some the patient s diagnosis was accepted

Brewster s first three studies concerned the same group of 572 patients with 77 controls treated with various antihista minics given in doses of 50 mg every four hours for at least three doses Actually results in only the 234 patients who were treated and the 22 controls who received a placebo within 12 hours of onset of symptoms were reported Data were cumulative A 90 per cent cure rate was reported for 21 pa tients given antihistaminics within one hour of onset of symp toms Only two controls were used for comparison in this group Of 234 patients treated within 12 hours or less after onset of symptoms 70 per cent were reported cured Criterion for cure was disappearance of all signs and symptoms within 24 hours of beginning treatment and for at least 48 hours after treatment was stopped The observation that treatment frequently had to be repeated at two to five day intervals sug gested to the Council that the original cold was not actually cured In interpreting the high percentage of cures (32 per cent) in a later series of 104 patients treated with placebos within six hours after onset of symptoms Brewster confirmed one of the criticisms of self diagnosis when he stated

allergic reactions manifested in the mucous membrane of the upper respiratory tract as the shock organ are quite common and self limited and account for the many times one believes he is catching a cold only to have it disappear without treat ment

Arminio and Sweet divided their work into two portions To determine whether daily administration of an antihista minic agent might prove effective in prophylaxis of common

(9) J A M A 142 566 569 F b 25 1950

cold they gave 50 mg daily 50 mg twice daily and 50 mg three times daily to each of three series of 100 patients As controls 300 other persons were given a placebo on the same schedules In these four groups the number of patients free from colds during the period of study were respectively 83 90 92 and 59 Though this study was more adequately controlled than others and results were statistically significant further verification is necessary To determine the effectiveness of an antihistaminic agent in common cold these authors gave 50 mg *three times* daily *Some controls* received a placebo and some the usual medicaments such as acetylsalicylic acid Average number of days for cure per patient was significantly lower in those given an antihistaminic This part of the study also was considered adequately controlled and statistically significant

All studies reported are not considered reliable however Reports now include 2 357 patients with common cold The diagnostic methods used have not conclusively demonstrated that the condition treated was common cold Over half the cases were investigated with inadequate controls or without controls and interpretations of results obtained are open to question Verification of the prophylactic value of these drugs is needed because the results are contrary to the experience of allergists Antihistaminics produce considerable subjective relief owing to inhibition of nasal discharge Similar results may be obtained with ephedrine or atropine Evidence so far presented should be classified as the honest opinion of the investigators and not as fact Further fundamental work is indicated to delineate clearly the influence of histamine in pathogenesis of common cold

Aureomycin in *Primary Atypical Pneumonia Controlled* Evaluation No previously available therapeutic agent has been found effective in primary atypical pneumonia Gordon Meiklejohn (Univ of California) and Robert I Shragg[1] (M C A U S) therefore conducted a study on parallel groups of patients one of which was given aureomycin All patients met the following criteria a clinical course and physical signs suggesting that the patient had primary atypical rather than bacterial pneumonia unequivocal roentgen evidence of pneu

(1) J A M A 140 391 396 May 28 1949

monia temperature of 102 F or higher during the 24 hours before institution of treatment a white blood cell count of less than 12,750 and significant improvement

The patients were first given an intravenous injection of 50 mg aureomycin hydrochloride in 5 ml of a leucine diluent which contained 131 mg l leucine in 5 ml and an oral dose of 1 Gm Thereafter they received 1 Gm of drug by mouth every 6 hours until temperatures had been normal for at least 48 hours Patients in the group not receiving aureomycin were given 100 000 units of aqueous penicillin every six hours

Prompt therapeutic response was observed in 22 patients treated with aureomycin Definite variation in duration of the disease was observed in the control group of 20 patients treated with penicillin Comparison of duration of fever in the *two groups indicates that penicillin is not an effective drug* and that aureomycin is highly effective in primary atypical pneumonia Apparent clinical relapse was observed in three patients after aureomycin therapy was stopped but each re sponded rapidly when treatment with the drug was resumed

[This study appears to have been carefully controlled The results are in agreement with tho e of others —Ed]

HERPETIC INFECTIONS

Acute Herpetic Gingivostomatitis in Adult is described by Arthur M Rogers Lewis L Corell Harvey Blank and Thomas F McNair Scott[2] (Univ of Pennsylvania) About 70 per cent of persons experience their first infection with the herpes simplex virus in infancy or early childhood This in fection is usually inapparent and can therefore be recognized as having occurred only by the presence of circulating anti bodies However in about 1 per cent of all infections the first attack by the virus can give rise to serious or even fatal dis ease These primary infections of which the commonest is the clinical entity known as acute herpetic gingivostomatitis are well recognized in childhood because they commonly occur in this age group In adult life however these clinical manifesta tions on the basis of the figures just quoted rarely occur and

(2) N w E gl d J Med 241 330 333 S pt 1 1949

therefore are liable to go unrecognized as herpetic infections The common adult manifestation is recurrent herpes labialis or fever blisters These recurrent attacks are usually accepted as being due to a reactivation by nonspecific stimuli of the herpes virus that has lain latent in the tissues of the host since recovery from the primary infection whether clinical or inapparent

The clinical features of primary herpetic infection that oc



Fig 6 —Appe e f m th f p t t n sxth d y f d e sh w g five phthou lc of m co m mbra a d o of m l b der G g a e r d d sw llen (Co te y f Roge s A M et l New E gla d J M d. 241 330 333 Sept 1 1949)

curred in three adults observed by the authors were similar to those previously reported in both children and adults No patient gave a history of previous fever blisters or canker sores and in two cases recent contact with a person who had a cold sore suggested a likely source of infection Chief complaints of the three patients were sore mouth fever and malaise Inspection of the oral cavity revealed some vesicular lesions but chiefly many small shallow discrete ulcers 1 5 mm in diameter (Fig 6) Gingivae were acutely inflamed along the margin Ulcerations were frequently present on the alveolar and palatal gingivae Regional lymph nodes were uniformly enlarged Temperature varied from 100 103 F (by mouth) returning to normal during the course of a week New lesions kept appearing in the mouth during the first few days and remained painful throughout the first week Healing

gradually occurred during the second week without scarring

Sudden onset of fever sore mouth and regional adenopathy in a previously healthy adult immediately presents a problem of differential diagnosis Diagnostic probabilities include Vincent s infection erythema multiforme infectious mononucleosis syphilis agranulocytosis acute leukemia pemphigus vulgaris and diphtheria of the pharyngeal or tonsillar region

Treatment is symptomatic Use of 1 per cent tetracaine hydrochloride or 2 per cent p aminobenzoyl dibutylamino propanol sulfate locally before meals affords added comfort Intense soreness of the gums makes brushing of the teeth impossible so that irrigation of the mouth is essential Penicillin should be used to control secondary infection by fusospirochetal organisms or pyogenic cocci

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VARICELLA

Clinical Observations on Use of Aureomycin in Varicella are reported by Milton M Mazursky Lydia Wright and Manfred Weichsel[3] (Willard Parker Hosp New York City) Eighty two patients aged 6 months to 12 years with varicella rash of less than 24 hours duration and none of whose lesions were in the crust or scab stage were examined on admission and followed daily for 6 days Aureomycin was administered orally (50 mg /kg body weight the first 24 hours 25 mg /kg the next 48) to 41 patients the other 41 served as controls Aureomycin had no effect on the patients treated Epidemic parotitis developed in two patients despite administration of aureomycin early in the incubation period

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RICKETTSIAL INFECTIONS

Cytology of Rickettsias In recent years it has been shown that all bacterial cells which have been adequately examined are essentially similar to cells of higher organisms with dem

(3) P d t cs 5 76-279 F bru y 1950

onstration of desoxyribonucleic acid containing regularly dividing nuclear structures and presence of ribonucleic acid in the cytoplasm Rickettsias are usually considered to be essentially like bacteria in morphology though they resemble viruses in being obligate intracellular parasites Electron micrographs have revealed some internal structures similar to those found in bacteria Chemical analysis of isolated rickettsias however has shown presence of desoxyribonucleic



F g 7 —Electron m crog aphs of icketts xtracted fr m yolk sacs s lfat p e p tat d and activated w th merth l t ® RCA U v sal l ct on m o cope ca × 15 000 (Co tesy of R H a d Fo J P J Exp r Med 89 681 686 J ne 1949)

acid only no ribonucleic acid having been detected Hans Ris and John P Fox[4] (Rockefeller Inst) attempted to determine whether ribonucleic acid could be demonstrated in unwashed rickettsias using cytochemical methods and whether the desoxyribonucleic acid was present in nuclear structures as in bacteria or was diffusely distributed through the rickettsial bodies

Internal structures of rickettsias seen with phase contrast microscopy and in the electron microscope contain desoxyribonucleic acid and are therefore nuclear structures similar to those found in bacteria They are minute spherical bodies either single as in spherical rickettsias or varying in number

(4) J Exper Med 89 681 686 J e 1949

from two to four in rod shaped forms (Fig 7) Occasional dumbbell shaped chromatinic bodies were thought to represent these structures in the process of division Presence of ribonucleic acid in the cytoplasm of rickettsias was demonstrated with use of ribonuclease and basic dyes The authors conclude therefore that rickettsias have a cellular organization similar to that of certain bacteria with a clear differentiation into nuclear structure and cytoplasm

Epidemiologic Studies on Q Fever in Southern California are reported by Joseph A Bell M Dorthy Beck and Robert J Huebner[5] When Q fever was discovered in the metropolitan area of Los Angeles in 1947 extensive studies were undertaken to determine the source of human infection It was found that cows and their raw products particularly milk were the most frequent sources and that these infections have caused an illness not heretofore recognized as Q fever in many persons Study of 300 cases in Los Angeles revealed that affected persons were rarely if ever the direct sources of infection for other persons and insects and arthropods played little if any role in spread of the disease to human beings An unusually large proportion of patients resided less than ¼ mile from a dairy or livestock yard had occupational contact with cows sheep or goats or their fresh products or used raw milk in their homes

Population groups of Los Angeles were selected so as to represent various degrees and types of ordinary contact of metropolitan persons with cattle and their products A rigidly standardized Bengtson (warm water bath 37 C) complement fixation technic was used uniformly Yolk sac antigens were prepared from the Henzerling strain of Coxiella burnetii at the National Institute of Health

To evaluate the significance of a positive reaction to this test serums of persons not located in Southern California were tested All persons who were definitely exposed to infection and in whom a proved infection developed and a few persons who were definitely exposed but had no clinical manifestations of the disease gave positive reactions to the test Practically all persons (99 8 per cent) not known to be exposed to infection had a negative reaction These include 1 150 per

(5) J A M A 14 868 872 M 25 1950

sons with various febrile illnesses not known to be Q fever 293 with positive reactions to the serologic test for syphilis and 862 having occupational contact with livestock and raw milk in Chicago The complement fixation test used was therefore highly specific for Q fever and all evidence indicated that a positive reaction means past infection with C burnetii

Among 5 000 persons selected as representative of the general population of Los Angeles the percentage of positive reactions was 1 36 per cent If this percentage is applied to the total population it indicates that over 50 000 persons in Los Angeles have been infected with C burnetii during the past several years Among patients selected because of some type of association with livestock or their raw products the percentage of positive reactions varied from nearly 4 per cent in packing plants slaughtering few or no young calves or dairy cows to 23 per cent in dairy workers A higher than normal per cent of positive serologic reactions was found in the following population groups (1) persons who had lived less than ¼ mile from a dairy or livestock yard (6 8 per cent in contrast to 5 1 per cent in persons living outside this distance) (2) persons who had occupational contact with cattle sheep or goats or with their raw products (9 1 per cent as against 3 per cent in those with no contact) (3) persons who had used raw milk (10 1 per cent in contrast to 4 2 per cent for nonusers) (4) recent residents of Los Angeles (1 5 per cent in contrast to 6 1 per cent among persons in longer residence) (5) persons under 40 (4 3 per cent versus 7 8 per cent in persons over 40) (6) persons with a history of illness with fever of two or more days duration diagnosed as pneumonia influenza or fever of undetermined origin (11 8 per cent in contrast to 5 per cent among persons who had no such history) Within industries handling livestock and their raw products those who had intimate and frequent contact with live or freshly killed dairy cows or their very young calves or certain raw products such as milk and hides had a higher proportion of positive reactions than those who had similar contact to a lesser degree

[The estimate that 50 000 cases have occurred in Los Angeles alone during the past several years points up the fact that a great many different diseases are labeled "grippe" or "flu"—Ed]

Chloramphenicol (Chloromycetin®) in Treatment of Tsutsugamushi Disease (Scrub Typhus) Joseph E Smadel Theodore E Woodward Herbert L Ley Jr and Raymond Lewthwaite[6] review their experience with chloramphenicol in treating 69 persons who contracted the disease in Malaya Results are compared with those in 19 patients who received only supportive therapy and 3 who were given para aminobenzoic acid No deaths occurred among the 69 given chloramphenicol although some were desperately ill when therapy was instituted Mortality among the 19 given only supportive therapy was slightly greater than 5 per cent Although clinical results with para aminobenzoic acid were less striking than those with chloramphenicol duration of the febrile period was reduced Para aminobenzoic acid appears to have a place in treatment of this disease when newer therapeutic agents are not available

Usually 6 Gm chloramphenicol was given orally over 24 hours Thirty of 32 patients who acquired the disease naturally were afebrile in an average of 32 hours irrespective of the stage of the disease when the drug was started These 30 patients convalesced rapidly and had no relapses In contrast of 37 volunteers who contracted scrub typhus relapses developed in 54 per cent These persons had been exposed for a number of days in hyperendemic areas during chemoprophylactic field trials The course of therapy given early in the disease to the volunteers was not adequate to control the infection permanently However the recrudescent disease was controlled without difficulty when chloramphenicol was again administered

The authors feel that additional information is needed before final conclusions can be drawn on what constitutes the optimal therapeutic regimen with chloramphenicol However it is recommended that all patients with scrub typhus irrespective of the time when treatment is started be given an initial oral dose of 60 mg /kg body weight and that this be followed by 0 25 Gm doses every 3 hours for at least 24 hours If recrudescent fever occurs course of treatment should be repeated No significant untoward effects were observed in any patients who received the drug

(6) J Cl[illegible] I[illegible] 28 1196 1215 S[illegible]pt[illegible]mb[illegible] 1949

NEUROTROPIC VIRAL INFECTIONS

Acute Lymphocytic Choriomeningitis Study of 21 Cases *About 150* supposed cases of acute lymphocytic choriomeningitis have been reported Because diagnosis can definitely be made only by virologic study many incompletely substantiated reports may have led to confusion regarding the natural history of the disease in man To describe more clearly the clinical picture produced by the disease William Roy Green Lewis K Sweet and Robert W Prichard[7] report 21 proved cases of acute lymphocytic choriomeningitis observed during 10 years at Gallinger Municipal Hospital

Virus of lymphocytic choriomeningitis has been reported to produce three types of clinical illness in man (1) systemic illness without central nervous system involvement (2) acute meningitis and (3) encephalitis The milder grippal illness has been proved only in laboratory experiments and in workers handling the virus and has been established in the general population only by demonstration of animal protecting antibodies in a considerable number of adults whose histories indicated no illness suggestive of meningitis In the reported cases *this type of illness* was not diagnosed nor was the encephalitic form diagnosed with certainty

Of the 21 patients aged 6 39 14 were females and 7 males The preponderance of adult females which has not been noted before lends support to the theory of the mouse reservoir of virus in transmission of the disease since women probably have closer contact with mice and their excreta in the home than do men The patients came from many social and economic levels and from varied types of dwellings In three instances mice infected with the virus were found in the patient s home

Headache was the commonest single complaint and was present in all patients On admission fever was present in all but one and all had stiffness of the neck Six were rational on admission *the others ranged from a cloudy to* a comatose state Total cerebrospinal fluid cell count varied

(7) J Ped t 35 688 701 D cembe 1949

from 142 to 3 370 on admission average being 1 179 cells A high cell count increased the likelihood of isolating a virus from that specimen Cerebrospinal fluid from all patients contained 90-100 per cent lymphocytes At initial and subsequent examinations spinal fluid dextrose was normal on all specimens from 14 patients in 7 one or more readings showed decreased dextrose content In 10 of the 16 instances in which protein determinations were done on initial spinal fluid specimens protein value was above 100 mg per cent One consequence of increased protein was formation of a pellicle a phenomenon which is erroneously regarded by some as pathognomonic of tuberculous meningitis White blood cell count varied from 4 800 to 10 000 with a normal differential count

In 19 of the patients the course of the disease was short self limited and benign in the sense that there were no residuals or deaths Severe and prolonged headaches with evidence of increased intracranial pressure which required periodic spinal punctures occurred in two Prognosis as to life and after effects was excellent

Differential diagnosis of lymphocytic choriomeningitis is complicated because of the many conditions which may produce a serous meningitis which is clinically similar to that caused by the virus of lymphocytic choriomeningitis Conditions which should be considered include

1 Viral
  a) Primary infection of central nervous system
    Lymphocytic choriomeningitis
    Poliomyelitis
    Encephalitis (various forms)
  b) Secondary infection (associated with rubeola epidemic parotitis varicella, rubella vaccinia etc.)
  c) Viruses that may invade the central nervous system (herpes simplex infectious mononucleosis lymphopathia venereum)
2 Bacterial
  Tuberculosis
  Infection with Hemophilus influenzae (rarely)
3 Spirochetal
  Syphilis
  We l s disease
4 Irritative
  Chronic inflammation imp nging on the meninges
5 Chem cal
  Lead poisoning
6 Fungus
  Torula

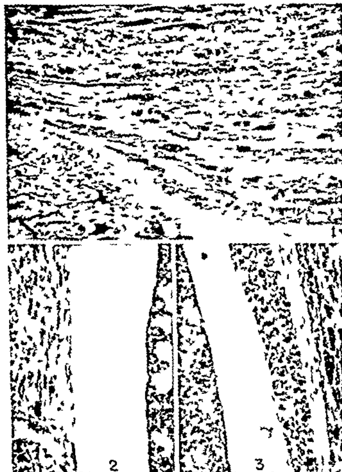
Acute Lymphocytic Choriomeningitis Study of 21 Cases About 150 supposed cases of acute lymphocytic choriomeningitis have been reported Because diagnosis can definitely be made only by virologic study many incompletely substantiated reports may have led to confusion regarding the natural history of the disease in man To describe more clearly the clinical picture produced by the disease William Roy Green Lewis K Sweet and Robert W Prichard[7] report 21 proved cases of acute lymphocytic choriomeningitis observed during 10 years at Gallinger Municipal Hospital

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(7) J Ped t 35 688 701 D mb 1949



F g 8—U l app n of muscl n p raly d s kl g m 1 m scl f leg 2 muscl f th wall 3 muscl f bd m nal wall (Court y f D lld f G *et al* J E pe M d 89 567 58 J 1949)

of 25 suckling mice and 2 suckling hamsters showed wide spread changes in the skeletal muscles of nearly all The le sion began as hyaline degeneration of the muscle fibers fol lowed by complete destruction The fibers were tran formed into amorphous masses the fragments being quickly absorbed

7 Protozoa
 Toxoplasmosis
8 Unknown etiology
 Serous meningitis in scarlet fever

[A valuable contribution Twenty one proved cases from a single hospital form an unusually large series There is an unfortunate tendency in many places to call any case of benign aseptic meningitis lymphocytic choriomeningitis Since the condition is a specific viral disease this term should be restricted to cases in which diagnosis is proved The outstanding laboratory finding is a spinal fluid cell count of several hundreds or thousands over 95 per cent of the cells being mononuclears —Ed]

Virus Recovered from Feces of "Poliomyelitis" Patients Pathogenic for Suckling Mice Gilbert Dalldorf Grace M Sickles Hildegard Plager and Rebecca Gifford[8] (New York State Dept of Health) report isolation of a virus from feces of children with symptoms similar to those of poliomyelitis However the agent differs from poliomyelitis virus in its host range in animals and anatomic response in the experimental animal to the virus is in striated muscles rather than in the central nervous system Original isolations were made from two children who lived in a Hudson River Valley village Six similar illnesses in this village were diagnosed as poliomyelitis

Recovery of a virus does not constitute proof that it has been responsible for the patient s disease unless an immune response to the agent is demonstrable Neutralization tests performed with acute and convalescent phase serums from the patients and the agents recovered from their feces revealed a neutralization activity which increased tenfold within 23 days and diminished in the following months It can be assumed therefore that both patients were infected with agents isolated from their feces at the time that they were ill

The agent was tested in mice hamsters guinea pigs monkeys and fertile hens eggs Of these only the first two showed signs of disease and mice were susceptible only in the first 12 days of life Incubation period of both strains of the virus was usually three days Gross lesions were not observed in viscera or organs of the central nervous system in infected mice but animals paralyzed for a day or more had opaque whitish muscles especially in the pectoral group the longissimus *dorsi* and in paralyzed extremities Severely paralyzed muscles were firm to touch and very white Histologic study

(8) J Exp r Med 89 567 58 J 1949

illnesses produced disease in newborn mice but not in monkeys Furthermore the strains recovered in newborn mice were tested in eight additional monkeys again with negative results Fecal samples from two patients with nonparalytic disease yielded poliomyelitis virus when inoculated into monkeys but did not produce disease in newborn mice

Tests for neutralization of the new virus with acute and



F g 9—Myos t n p ly d l mb of 8 day ld mou k ll d on fi t d y of p ly edu d f om × 155 An mal wa ocul t d by nt br l nd tra bd m nal out w th n 24 hou fte b rth (Courte y f Meln ck J L et l P oc Soc E p B l & M d. 71 344 349 J ly 1949)

convalescent serums of the patients revealed that the serums of seven patients from whom the new agent was isolated neutralized the virus (neutralization index from 1 000 10 000) in the convalescent stage and to a lesser degree in the acute stage Convalescent serums of five other patients with nonparalytic illnesses also neutralized the virus Convalescent serums of the three patients diagnosed as having paralytic poliomyelitis and the serum of the two nonparalytic patients from whom poliomyelitis virus was isolated all failed to neutralize the virus

Swiss mice generally between 1 and 2 days of age were

and phagocytosed (Fig 8) Regeneration was evident from the first and large masses of young actively multiplying muscle cells gave the lesion a cellular appearance

Agents that induce similar signs and lesions in suckling mice have been isolated during other outbreaks and from isolated cases of apparent poliomyelitis Other known viruses that induce similar lesions in striated muscles do not selectively paralyze suckling mice and do induce lesions of the central nervous system Immune animal serums for Newcastle disease lymphocytic choriomeningitis the Aycock and Lansing strains of poliomyelitis and the MM virus failed to neutralize the new agent as did serums of adult normal mice and rabbits Isolations of the new agent to date have all been from patients with a diagnosis of abortive or paralytic poliomyelitis but since no effort has been made to recover virus from patients with other diseases or from healthy persons no conclusions based on the association seem warranted

[This and the succeeding three articles are concerned with a newly discovered virus now called Coxsackie or C virus Its presence in the stools of patients with aseptic meningitis or poliomyelitis like disease has aroused great interest. There is however no convincing evidence to date that the virus causes disease in man —Ed]

Virus Isolated from Patients Diagnosed as Nonparalytic Poliomyelitis or Aseptic Meningitis Joseph L Melnick Ernest W Shaw and Edward C Curnen[9] (Yale Univ) describe isolation of a filtrable agent from patients with an illness resembling nonparalytic poliomyelitis which occurred during 1948 in southern New England The agent is similar to that reported by Dalldorf and Sickles Like their agent the virus infected newborn albino mice and produced weakness and paralysis accompanied by diffuse myositis

During the summer and fall of 1948 samples of feces were collected from 16 representative patients from Connecticut and Rhode Island 13 of whom had clinical features consistent with nonparalytic poliomyelitis and 3 of whom had definite muscle weakness and were diagnosed as having paralytic poliomyelitis Fecal samples were tested in monkeys for poliomyelitis virus and were also examined for the agent infectious for newborn mice

Fecal samples from five of the patients with nonparalytic

(9) Proc. Soc Expe B 1 & Med 71 344 349 J ly 1949

that not all cases included had been caused by the same agent The second alternative appeared to be substantiated by laboratory evidence

An attempt was made to determine the cause of illness in 14 patients without paralysis Strains of a filtrable virus which caused fatal paralysis in infant mice but did not produce apparent disease in monkeys or older mice were recovered from feces obtained during the first two weeks of illness from 5 of the 14 patients Specimens of serum obtained from these and from five more patients during illness or after recovery neutralized a strain (Connecticut 5) of the new virus which had been isolated from one of the patients Suspensions of feces from each of two other patients produced poliomyelitis in monkeys and failed to cause disease in infant mice Specimens of serum obtained from each of these patients during or after illness failed to neutralize the Connecticut 5 strain of C virus Laboratory observations on these two supported the diagnosis of nonparalytic poliomyelitis

Suspensions of feces from another two patients failed to produce disease in either monkeys or infant mice and serum from these patients also failed to neutralize the Connecticut 5 strain of C virus The nature of the causative agent in these two cases was not established

Virus pathogenic for infant mice was also found in feces of individual patients in Ohio who had nonparalytic illnesses during the summer of 1948 As reported previously strains of C virus have been found in pooled human feces collected during 1947 in Akron O and in 1948 in Winston Salem N C as well as in samples of sewage collected in 1948 from six cities three in Connecticut and three in North Carolina This indicates that strains of virus pathogenic for infant mice are widely distributed in nature

The clinical features of illness in 10 patients with the syndrome of aseptic meningitis or nonparalytic poliomyelitis from whom the C virus was isolated or whose serum neutralized it were analyzed Onset of illness was gradual in seven and relatively abrupt in three Prodromal constitutional symptoms generally preceded those suggestive of meningeal irritation In each of the patients fever developed in all but one on the first day of illness Headache nausea and abdominal pain

used They were inoculated intracerebrally and/or intraperitoneally Signs of disease appeared within 2 10 days manifested by weakness and paralysis of one or more extremities and followed by death generally within 24 hours The outstanding pathologic change was extensive myositis in skeletal muscles especially of the limbs (Fig 9) Preliminary data on sedimentation suggest that the agent is one of the smaller viruses

A physician working with this agent had a vague febrile illness of eight days duration which was diagnosed as fever of unknown origin The only suggestion of central nervous system involvement was minimal back stiffness Virus was recovered from feces and nasopharyngeal washings during the acute illness Neutralizing antibodies were not found during the acute phase but appeared in increasing titer during convalescence

The virus was widespread in this country during the summer of 1948 having also been isolated from sewage of a number of cities and from flies collected in widely separated areas

Disease Resembling Nonparalytic Poliomyelitis Associated with Virus Pathogenic for Infant Mice is described by Edward C Curnen Ernest W Shaw and Joseph L Melnick[1] (Yale Univ) Because of an unusual number of patients with illnesses resembling nonparalytic poliomyelitis admitted to hospitals in southern New England during the summer of 1948 and because observations indicated the existence of a new infectious agent associated with illnesses resembling poliomyelitis further investigations of the agent and the illnesses with which it appeared to be associated were made

A total of 157 patients with a diagnosis of poliomyelitis or aseptic meningitis cause unknown was studied Of these 44 were classified as having paralytic and 113 as having nonparalytic infections Analysis based on date of onset of each patient s illness showed that the highest incidence of nonparalytic cases was in August and of paralytic cases in September and October The difference in distribution was statistically significant This observation indicated either that cases of paralytic and nonparalytic forms of infection with poliomyelitis virus had different seasonal distribution curves or

(1) J A M A 141 894 900 Nov 6 1949

Positive observations were limited to fever (101 103 F) moderate redness of the oral pharynx and stiffness of the neck Spinal fluids were clear with elevated cell counts and lymphocytes predominated averaging 154/cu mm Spinal fluid protein was increased in each case and averaged 65 mg /100 cc Sugar and chloride levels and manometric pressures were normal as were stained smears and cultures of spinal fluid Recovery was rapid and convalescence uneventful Average hospital stay was 13 days

Because these cases occurred at the height of the expected poliomyelitis season in a year of increased incidence of poliomyelitis in the United States the diagnosis of abortive or non paralytic poliomyelitis was strongly suspected Since it is possible to detect the poliomyelitis virus most easily from stools stool specimens obtained from 10 patients during the first two days of acute febrile illness were submitted to the Yale virus laboratory Specimens were reported negative All other possible viruses included in differential diagnosis were ruled out and the etiologic agent was determined to be a new virus by processes of exclusion and clinical evaluation and by virus studies performed at the Yale virus laboratory and that at Bethesda Md

Mumps Meningoencephalitis with and without Parotitis is discussed by Lawrence Kilham[3] (Harvard Univ) Only recently have clinical and epidemiologic observations concerning this disease been confirmed by adequate diagnostic laboratory evidence despite general recognition that clinical manifestations are not always pathognomonic In the present study of 25 patients with mumps meningoencephalitis 13 with no salivary gland enlargement conclusions were based on cases diagnosed by a combination of the newer technics of serologic study and virus isolation The patients were followed in two Boston hospitals in 1948 a year particularly suited to the study because of the unusual prevalence of mumps in Massachusetts

In these 25 patients meningeal irritation was variously manifest by headache nausea vomiting and nuchal rigidity A few children had convulsions and delirium One significant feature was the impossibility of distinguishing clinically be

(3) Am J D Ch ld 78 3 4 333 Sept mber 1949

stiffness of the neck or back and pain in one or more extremities were noted frequently Stiffness of the neck or back led to hospitalization in most instances All patients were rational and co operative Fever lasted 1 10 days Hyperemia of the pharynx was noted in seven patients There were no abnormalities of cerebrospinal fluid pressure Total leukocyte counts in spinal fluid ranged from 27 to 600 in all but one patient counts were less than 150 Percentage of polymorphonuclear cells in spinal fluid ranged from 0 to 74 Total leukocyte counts in blood were usually normal The course of illness was relatively brief

In other patients from whose feces strains of the new virus were recovered abdominal or thoracic pain was the most prominent symptom One patient had an illness considered to be epidemic pleurodynia Three laboratory workers in whom the illness developed while they studied the C virus had abdominal and thoracic pain chiefly and no signs suggesting meningeal or central nervous system involvement All three recovered completely

It appears that strains of a virus pathogenic for infant mice are widely distributed in nature and that in man acute illnesses associated with this agent may resemble poliomyelitis epidemic pleurodynia or mild undifferentiated fever

Aseptic Meningitis of New Virus Origin Series of 18 Cases is reported by Alexander A Jaworski and Edward J West[7] (Charles V Chapin Hosp Providence R I) This series is noteworthy because at no time in the past were patients with similar cases of aseptic meningitis ever admitted to the hospital By method of exclusion relying heavily on extensive laboratory virus studies the etiologic agent was shown to be a new virus affecting the meninges in a mild and typical manner

Histories of the illness were similar Manifestations were typical of meningeal irritation headache moderate aching and stiffness of the neck and occasional vomiting All patients experienced the generalized effects of any acute illness namely fever minimal anorexia and general malaise Patients were alert and co operative when hospitalized complaining chiefly of severe diffuse headache and moderate malaise

(7) *J A M A* 141 90 904 Nov 26 1949

antihemagglutination test is simple and as satisfactory as complement fixation in establishing a diagnosis of mumps A serologic test is indicated whenever appropriate signs and symptoms are associated with a spinal fluid having 150 2 500 leukocytes/cu mm of which 95 per cent are lymphocytes and an elevated total protein content and especially with a history of exposure to mumps Successful isolation of mumps virus gives additional confirmation A high titer of mumps antibody in a single convalescent phase serum may be mis leading Among patients with encephalitis serving as controls because of clinical differences in some and uniform failure to isolate mumps virus a number had a high level of anti bodies in both acute and convalescent phase serums Acute phase serum should be obtained as early as possible prefer ably within a few days of onset because mumps antibodies are often present when active symptoms first appear Virus isolation from cerebrospinal fluid has been accomplished in only a few types of encephalitis of known origin It has been demonstrated here however that virus can be isolated in 50 per cent or more of spinal fluids taken in the first week of mumps meningoencephalitis

[Development of a serologic method to detect mumps virus infection has established the fact that it is one of the commonest if not the com monest cause of benign aseptic meningitis The spinal fluid findings are similar to those of lymphocytic choriomeningitis —Ed.]

Nonparalytic Poliomyelitis and Mumps Meningoencepha litis Differential Diagnosis Since development of the comple ment fixation test for diagnosis of mumps infection some in vestigators have obtained positive reactions for mumps with serums of patients who on clinical and epidemiologic grounds were regarded as having nonparalytic poliomyelitis Lawrence Kilham Jeanette Levens and John F Enders[4] (Boston) there fore carried out mumps complement fixation and inhibition of hemagglutination (antihemagglutinin) tests on pairs of serum specimens from 17 patients in acute and convalescent stages of illness diagnosed either tentatively or finally as nonpara lytic poliomyelitis All cases occurred from July through Oc tober 1948 From serologic tests it was concluded that in 6 of the 17 cases the mumps virus was responsible for the dis ease During the illness in all cases a significant increase in

(4) J A M A 140 934 936 J ly 16 1949

tween signs and symptoms of patients with mumps meningo encephalitis and those of others who had serologically nega tive reactions for mumps and such clinical diagnoses as non paralytic poliomyelitis and lymphocytic meningitis

A few patients had sequelae One had weakness of the an terior part of the neck and abdominal muscles when seen later in a clinic for after care of poliomyelitis Another had weak ness of a leg for a few weeks after discharge Two patients were judged to have personality changes as a result of their illnesses Ages of patients ranged from 1 to 35 years

A pronounced pleocytosis with a high percentage of lymphocytes characterized the spinal fluid of the patients with mumps meningoencephalitis Leukocyte counts exceeded 300/cu mm in 19 instances and were over 1 000/cu mm in 9 No count fell below 100/cu mm in the first week of the dis ease Every patient showed a percentage of lymphocytes of 95 or greater at some time although 4 of the 64 spinal fluids examined had percentages slightly below this figure

Antihemagglutination and the complement fixation tests gave comparable results One or both tests showed a fourfold and usually a greater increase in antibodies when serums of the acute and convalescent phases were compared for all pa tients Of 21 attempts to isolate mumps virus from patients with clinical mumps meningoencephalitis all were successful Mumps virus was isolated from the spinal fluid of more than half the patients with confirmed mumps infection of the cen tral nervous system Twelve patients served as controls for the group with serologically proved mumps meningoencepha litis six with uncomplicated mumps parotitis and six with disease of the central nervous system determined not to be mumps by serologic tests In no instance was mumps virus isolated from spinal fluids of the controls

Mumps meningoencephalitis with or without parotitis is in certain years a *common form of lymphocytic meningo* encephalitis among children and young adults Knowledge of the true incidence of this disease especially when no glandular swelling is apparent will await further application of newer diagnostic methods to a study of epidemics of mumps occurring within closed groups No other encephalitis can be identified more readily by serologic methods for the

transient psychic changes optic neuritis persistent hemiplegia and damage to the acoustic and vestibular nerves It is therefore surprising that the prognosis of mumps meningoencephalitis is considered to be so good and that on the whole the significance of mumps virus infection relative to possible damage to the nervous system is overlooked

During the spring of 1947 a follow up was carried out at Stockholm Epidemic Hospital on all patients treated for mump meningoencephalitis during 1942-44 Of a total of 75 patients 39 were found to be symptom free The remaining 36 reported such symptoms as fatigue headache and dizziness in 11 symptoms could be ascribed to other affections of the nervous system but 15 were considered to have definite sequelae of meningoencephalitis Ten could not be classified with certainty

The 15 patients with definite sequelae were divided into two groups (1) 10 patients in whom it was possible objectively to verify the symptoms and (2) 5 who had symptoms partly of a psychic nature (irritability defective memory impaired concentration power) and partly consisting of headaches and fatigue the symptoms coinciding with onset of meningitis with no other explanation established In only a few instances were the sequelae relatively severe one child had total unilateral deafness another had severe epilepsy one man had vestibular dizziness Sequelae in other patients were milder though a constant source of irritation There were diverse mild forms of eye and ear symptoms some mental symptoms of a neurasthenic nature both with and without headache and one or two cases of endogenous obesity possibly from injury to the hypothalamus *In a few patients* electroencephalographic changes were noted

It was concluded that permanent ill effects after mumps meningoencephalitis are more likely when distinct symptoms of encephalitis are present at the acute stage However no connection between cerebrospinal fluid findings in the acute stage and later symptoms could be demonstrated

Measles Encephalitis Study of 50 Cases *During* the winter and spring of 1946 there was a severe epidemic of measles in Philadelphia Among the 13 037 reported cases as far as can be ascertained were 14 of measles encephalitis a ratio of

complement fixing antibody (eight times or more) was dem onstrated A comparable increase in antihemagglutinins was also revealed Confirmatory of the serologic observations was demonstration of virus in spinal fluid specimens obtained in three cases Serologic tests in the other 11 cases failed to show any change in concentration of mumps antibody during the disease

Leukocyte counts of the cerebrospinal fluid in the six cases of mumps meningoencephalitis all exceeded 200/cu mm and the proportion of lymphocytes was at least 90 per cent In four of them total protein exceeded 40 mg /100 cc In contrast in most cases in which mumps virus was not involved there were lower total protein concentrations and leukocyte counts

These studies indicate that the disease in 6 of 17 patients *diagnosed clinically as having nonparalytic poliomyelitis* was actually infection with mumps virus without salivary gland involvement Although the number of patients is small these observations are sufficient to show that it is often impossible to identify the nature of the infectious agent in either of these conditions on clinical and epidemiologic criteria alone Since mumps meningoencephalitis without parotitis is by no means rare it seems that whenever possible diagnosis of nonpara lytic poliomyelitis should be withheld until laboratory tests for mumps meningoencephalitis have been carried out

From the epidemiologic viewpoint diagnosis of nonpara lytic poliomyelitis may be suggested if other members of a family or group concurrently have the paralytic form With out a definite history of this sort however the mere occur rence of aseptic lymphocytic meningoencephalitis during the late summer and early fall when poliomyelitis may be epi demic is insufficient to warrant even a tentative diagnosis of the nonparalytic form of the disease

Sequelae of Mumps Meningoencephalitis were studied by Vera Oldfelt (Linkoping Sweden) It is thought by some that mumps is always accompanied by some degree of encepha litis Although it is generally believed that no appreciable neurologic sequelae occur in patients with meningeal signs complicating mumps grave sequelae occur with the more typical forms of encephalitis Residual conditions include

(5) Acta med Sca d a 134 405 414 1949

pared with those of nondehydrating therapy the small difference in percentage of mortality was obviously not statistically significant Clinical impression was that in certain instances dehydration therapy prevented further involvement of the brain but this was not so in every case

Several theories have been proposed concerning the complication of measles with encephalitis (1) that it is due to the virus of measles (2) that it is an allergic or anaphylactic phenomenon and (3) that it is caused by an unknown virus separate and distinct from that of measles It is difficult to prove any of these theories but there is strong evidence that the virus of measles is the same as that causing encephalitis

[A tragic but fortunately rare complication —Ed]

Motor Manifestations of Herpes Zoster Report of Case of Associated Permanent Paralysis of Phrenic Nerve is made by Seymour Lionel Halpern (Tufts College) and Albert H Covner[7] (Lynn Mass Hosp) The frequent involvement of the anterior horn in herpes zoster even though no external paralysis is evident has now been established Viral origin of herpes zoster has been conclusively established and the organism is thought to be closely related to the virus of varicella On reaching the nervous system probably as an ascending myelitis the virus causes diffuse damage It usually attacks one or two segments most vigorously destroying the posterior ganglion on the same level and travels down to the skin causing the characteristic eruption A ca e is presented in which motor manifestations were an integral part of the neurodermatologic disorder zoster

Man 53 had typical zoster involving th third and fourth cervical segments on the right side Three days after the eruption reached its maximum shortness of breath developed but there was no cough or pain in the chest He was treated variou ly for neurasthenia and potential cardiac di ease for a year His only complaint was of dyspnea especially on exertion but also after meals and on bending over It was found that the right side of the diaphragm failed to de cend on deep in piration Fluoroscopic examination revealed that the right diaphragm rose on inspiration and descended on expiration There was no evidence of bone destruction in the cervi al portion of the spine Ga trointestinal work up revealed no paralysis of the swallowing reflex no evidence of compression dilatation or other abnormalities in the esophagus or in

( ) A h I t M d 84 907 916 D ember 1949

1 1 000 reported cases Steven Sawchuk, Alfred C LaBoccetta Anthony Tornay Alexander Silverstein and Augustin R Peale[6] reviewed cases of the last 50 patients with measles encephalitis including those of 1946 treated at Philadelphia Hospital for Contagious Diseases and report results of follow up neurologic and psychologic examination Interim from date of disease to time of follow up varied from one month to several years Of the 50 patients 16 died in acute stages of the disease and 34 survived Of the survivors 19 returned for examination and family physicians reported on 3 others Thus 22 were available for analysis

Diagnosis of measles encephalitis was based on coma convulsions stupor or drowsiness with or without cerebrospinal fluid changes Many patients had complications in addition to measles encephalitis Of 18 patients with associated pneumonia 8 died (44 4 per cent)

Distribution of patients according to cerebrospinal fluid cell count revealed 29 with 50 cells or less There were 11 deaths in this group (38 per cent) the highest death rate among all groups It may be assumed therefore, that a low cerebrospinal fluid cell count in measles encephalitis indicates a grave prognosis Even more significant is the fact that 75 8 per cent of deaths in patients with a low cell count occurred in the group with less than 25 cells Six patients showed abnormality of gait caused by cerebellar ataxia in one involvement of the pyramidal tract in another and lower motor neuron lesions in four Of 13 patients examined only 4 had normal electroencephalograms No specific characteristic pattern was seen in EEG s of patients with encephalitis but in general records were characterized by slow abnormal high voltage waves (sharp and slow waves) with a frequency of 2 3 or 4/second

Because clinical and autopsy observations suggested that brain edema was responsible in great measure for symptoms and death in several patients dehydration therapy was tried comprising limitation of fluids orally and administration of hypertonic glucose solution intravenously hypertonic magnesium sulfate enemas and concentrated human plasma intravenously When results of dehydration therapy were com

(6) Am J D Ch ld. 78 844 867 Decemb 1949

munity to chickenpox Because of the relative rarity of the simultaneous occurrence of the two diseases Ferdinand Fetter and Truman G Schnabel[8] (Presbyterian Hosp Philadelphia) report the following case

Woman 72 was hospitalized because of herpes zoster of the right side at the level of the eleventh and twelfth thoracic ganglions There was a florid eruption of coalescent vesicles over the lower right side of the chest and extending across the right flank to the upper right side of the abdomen Aside from the herpes physical examination showed nothing significant Two days after admission a few papules and vesicles were noted on the scalp face neck chest and abdomen and there was slight temperature elevation On the following day the number of cutaneous lesions had increased tremendously and some of the vesicles had become pustular with umbilicated centers The eruption was entirely typical of chickenpox The patient had not had that disease before and there was no history of recent exposure to chickenpox or of contact with a patient with herpes zoster

The generalized eruption of varicella subsided after 10 days but the herpes zoster ran a protracted course despite roentgen therapy and large doses of thiamine hydrochloride The cutaneous lesions did not involute until almost two months after onset and severe pain persisted after that

[Evidence continues to accumulate that these two diseases are caused by the same virus —Ed]

Aureomycin Treatment of Herpes Zoster was investigated by Maxwell Finland Edmund F Finnerty Jr Harvey S Collins John W Baird Thomas M Gocke and Edward H Kass[9] (Boston) Aureomycin and chloromycetin® (chloramphenicol) are generally referred to as agents effective against viral infections Yet their demonstrated therapeutic action has been limited to rickettsial diseases infections with the psittacosis lymphogranuloma venereum group and primary atypical pneumonias (aureomycin only) Neither agent has been proved effective against true viruses such as those which cause yellow fever influenza poliomyelitis or encephalitides Recently beneficial effects have been claimed for these antibiotics in certain skin diseases thought to be due to viral agents among which is herpes zoster Regarding etiology of herpes zoster human skin grafts on the chorioallantois of chick embryos have been successfully infected with vesicle fluid from a patient with herpes zoster and elementary

(8) A h I t M d 83 502 504 M y 1949
(9) N w E gl d J M d 241 1037 1047 D 29 1949

the remainder of the gastrointestinal tract and no signs of hiatus hernia Diagnosis therefore was exertional dyspnea caused by paralysis of the diaphragm secondary to paralysis of the phrenic nerve associated with zoster

Paralysis of the phrenic nerve as a motor manifestation of zoster has not previously been reported Despite frequent involvement of the anterior gray matter motor manifestations are not detected as often as expected because not all the anterior horns are necessary for normal motor function It is recommended that every patient with zoster be scrutinized for motor manifestations so that (1) the true incidence of motor manifestations can become known (2) criteria for diagnosing unusual cases of muscular paresis due to herpes zoster with or without neuralgias, can be established (3) errors in diagnosis can be avoided

[I have observed marked quadriceps weakness in a patient with herpes zoster on the thigh —Ed]

Concurrent Herpes Zoster and Chickenpox Report of Case The relation between herpes zoster and chickenpox was first pointed out over 60 years ago when the latter disease was reported in members of two families after episodes of herpes zoster in other members In 1917 one author found in the literature reports of 37 cases of chickenpox occurring after exposure to herpes zoster In all these cases chicken pox followed the herpes zoster in two to four days This author concluded that the two eruptions represent different phases of the same disease and advised that herpes zoster be made a quarantinable disease to prevent development of chickenpox in persons contacted by patients

In the recent literature there is a report of the simultaneous occurrence of the two diseases in a man aged 31 *The author pointed out that there is some evidence that* chickenpox in childhood makes a person immune to herpes zoster in later life and that herpes when it occurs in an adult represents a partial immunity to the chickenpox virus in a person who has never become fully immunized by having the disease This line of reasoning leads to the conclusion that the viruses of chickenpox and herpes zoster must be either identical or closely related and the rare cases of the two diseases occurring simultaneously can be explained by increased virulence of the virus sufficient to overcome the partial im

[The authors are properly cautious in interpreting their results Others have had even less encouraging experience Herpe zo ter is re ported to have developed in one patient while he was receiving aureomy cin for another disease —Ed.]

Occurrence of Herpes Zoster in Carcinoma of Breast. It is common knowledge among oncologists and radiotherapists that incidence of herpes zoster in *Hodgkin s* disease leukemia and metastatic carcinoma is greater than in the population at large although statistics on the subject are not available Eugene P Pendergrass and David Kirsh[1] (Univ of Pennsyl vania Hosp) therefore investigated the records of 406 pa tients with breast carcinoma seen between 1932 and 1939 Six teen were found to have had herpes zoster 12 of whom had evidence of metastases either before or after appearance of the cutaneous disease The other four survived between 6 and 12 years after the herpetic attack with no evidence of metas tases

Fourteen of the patients with herpes received pre or post operative roentgen irradiation or both only 2 received no irradiation Since all patients died at home no autopsy studies were available However it is hoped that by calling attention to the relatively high incidence of herpes zoster in breast car cinoma this as ociation will be noted more carefully in the future and that clinicopathologic studies particularly of the spinal cord may reveal the etiologic factors Too often lesions of herpes zoster are noted merely in passing with no attention to the dermatomes involved and the possible relation to under lying neoplastic or inflammatory process

The authors conclude that herpes zoster occurs in rela tively high incidence in breast carcinoma especially in cases with metastases The etiologic significance of irradiation and metastases needs to be clarified

[Other di ease in which there eems to be an association include the lymphomas spinal cord tumor and tuberculous meningitis —Ed]

Rabies Vaccine Encephalomyelitis in Relation to Incidence of Animal Rabies in Los Angeles is discussed by Charles F Pait and Harold E Pearson[2] In Los Angeles City and County about 200 rabid dogs are detected annually Only one person a year develops rabies but at least 800 persons are given rabies vaccine The chance of acquiring rabies from known dog bites

(1) Am J M S 217 674 680 Jun, 1949
(2) Am J P b He lth 39 8 5 8 7 J ly 1949

bodies have been demonstrated by electron microscopy in the vesicle fluid from various clinical types of herpes zoster lesions The authors report results of aureomycin treatment in 24 cases of herpes zoster Although a specific therapeutic effect was not demonstrated beyond any reasonable doubt results were encouraging

There were 15 men and 9 women aged 23 85 mostly in the older age groups Three patients in the initial stage of infection were given aureomycin beginning on the second to fourth day 14 others in the acute stage were first treated between the second and seventh day In all but 2 of these 17 patients lesions and symptoms began to show definite improvement after the first 24 hours of therapy Three patients treated between 10 and 14 days responded well to therapy Four were treated late in the disease In three aureomycin was started between 14 and 21 days and lesions began to heal and pain subsided promptly in the fourth treatment was started with *small doses during the fifth week with little effect* Best results were obtained in patients treated on or before the middle of the second week after appearance of symptoms or lesions New lesions did not appear after the first day of therapy Pain then subsided lesions dried up and healing progressed rapidly When treatment was interrupted early new lesions soon appeared and pain recurred the disease process was again arrested by resumption of therapy Occasionally post herpetic pain appeared despite early and adequate treatment The dose recommended is 4 Gm daily until lesions show signs of definite healing (usually two to four days) and then 2 Gm daily for three to five days

Evidence presented strongly suggests that aureomycin has a definite beneficial effect in herpes zoster It is emphasized that although these results were obtained in consecutive cases no parallel control series was observed The feature that suggested a beneficial if not specific effect was the fairly regular and characteristic response in all patients who received adequate aureomycin in the early or active stage However herpes zoster has been observed to develop during aureomycin treatment for other infections Therefore the estimate of the specific value of aureomycin in herpes zoster as suggested by this series may have to be revised

of illness during the entire observation period The Flury strain was therefore inoculated into the upper quadrant of the posterior surface of thigh muscles of 12 dogs No dog showed a rise in body temperature or any signs of local reaction during the three weeks after inoculation nor were there any systemic reactions during a six months observation period It was concluded that intramuscular inoculation of the Flury virus appeared to be completely innocuous to dogs

Before attempting to study the immunologic response of dogs to challenge with street virus after parenteral introduction of the Flury strain it was imperative to determine the pathogenicity for dogs of the street virus used in the laboratory (the NYC strain) The NYC strain had been isolated from the salivary gland of a rabid dog in New York City and had been maintained by inoculating dogs bilaterally into the masseter muscles with a suspension of infected salivary glands When the NYC street strain was used over half the inoculated dogs died of rabies On the basis of these results the authors considered it appropriate to use the NYC strain for challenge purposes bearing in mind that though results of individual tests may be of meager statistical value combined results of many tests may be statistically satisfactory

Dogs were inoculated with a single injection of chick embryo suspension at various egg passage levels of the Flury strain Only 2 of 76 vaccinated dogs died after challenge as compared with 32 deaths among 46 nonvaccinated controls These favorable results encouraged further investigation into the possibility of utilizing the Flury strain as an immunizing agent for dogs Preliminary results of such studies indicate that dogs inoculated with the Flury strain are resistant in almost all instances to challenge with the virulent street strain of rabies virus Data on duration of immunity after vaccination with the Flury strain are incomplete the longest interval between vaccination and challenge being only 27 weeks However evidence presented by others indicates that immunity after vaccination with live rabies virus is long lasting

It is concluded that the Flury strain vaccines administered to dogs parenterally are devoid of pathogenic properties Immunizing power of the vaccines as tested in 76 dogs was excellent The number of dogs so far inoculated intramuscu

in Los Angeles is estimated to vary from 1 1 400 to 1 2000 During 1940-46 there were nine cases (one fatal) of post vaccinal encephalomyelitis among 5 500 treated persons an incidence of 1 600

On the basis of such data it is apparent that incidence of rabies vaccine encephalitis is a real contraindication to the indiscriminate use of the vaccine It is likely that incidence will be reduced greatly when a product more completely puri fied of brain tissue is produced most present vaccines consist of about 10 per cent suspensions of rabbit brain

There is ample evidence that rabies can be controlled in the absence of any considerable wild animal reservoir by con trol of dogs No program of control can be effective unless ac cepted by the public This aspect is complicated in the Los Angeles area by presence of dog fanciers who tend to resist all efforts to interfere in any way with the dog population While such persons may reject programs based on protection of human beings *they can scarcely fail to accept one designed primarily for protection of dogs*

[Rabies vaccine should not be given unless the skin has been pene trated by a bite The treatment carries with it risk not only of en cephalomyelitis but also of other allergic reactions skin eruption fever malaise —Ed]

Studies on Chick Embryo Adapted Rabies Virus Patho genicity for Dogs and Use of Egg Adapted Strains for Vac cination Purposes Previous communications have dealt with the adaptation of several strains of rabies virus to fertile hens' eggs and the pathogenicity of the egg adapted strains for dif ferent species of animals In the present study Hilary Kop rowski and Jack Black[3] (Pearl River N Y) consider sus ceptibility of dogs to the egg adapted strains of rabies virus and report immunization experiments with dogs The Flury strain of rabies virus was chosen because it had displayed a lower degree of pathogenicity for experimental animals than other egg adapted strains of rabies To determine whether it remained pathogenic when introduced parenterally the mas seter route of inoculation was selected for preliminary tests with the expectation that if the strain proved nonpathogenic *by that route* parenteral inoculations by other routes certainly would be harmless None of the inoculated dogs showed signs

(3) J Imm 1 64 185 196 M h 1950

In several experiments no beneficial effect was noted from vaccine treatment By contrast one injection of antiserum even in 1 16 dilution protected most animals infected with 1 160 dilution of virus and antiserum in 1 32 dilution showed the same protective power for animals infected with 1 320 dilution Treatment with vaccine (Semple) gave no protection as indicated by identical mortality ratios with untreated control animals When antiserum alone was administered 24 hours after infection to 10 rabies infected hamsters only 1 died of rabies When the same type of antiserum treatment was followed by a 14 day course of phenolized vaccine results were equivocal although more hamsters did die in the antiserum vaccine treated groups Thus it is possible that vaccine may have exerted some depreciative effect on antiserum therapy in hamsters Similar studies were made on guinea pigs

Antiserum has been given to 20 human beings because of bites from animals suspected to be rabid because of probable exposure to rabies or after a laboratory accident Seven patients were definitely exposed i e either the animal which inflicted the wound was found to be rabid or the laboratory material contained street virus All patients were given 1 1 5 ml /kg body weight of antiserum concentrate intramuscularly and all but two were treated within 24 hours after exposure Only one patient who twice received a full course of Pasteur s treatment before the current exposure was given antiserum alone All other patients were given either a short course of vaccine or intensive vaccine treatment after antiserum treatment None of the patients subsequently showed any signs of rabies

The authors conclude that vaccination of hamsters or guinea pigs with phenolized rabies vaccine preparations is of little avail after exposure In contrast antiserum concentrate seemed in all instances to exert a definite protective power after exposure In hamsters and guinea pigs the incubation period of experimental street rabies is 13-22 days Only rarely will an animal show signs of illness later than 30 days after exposure and the statistically insignificant number of such instances does not permit evaluation of any form of treatment Since an incubation period of rabies of less than 30 days occurs in man only with severe exposure it is not possible to

larly with the Flury strain is not insignificant therefore bar ring unforeseen and unexpected changes it may safely be as sumed that the strain is innocuous for the canine species when introduced parenterally Advantages of egg adapted living virus for vaccination purposes in dogs are (1) apparent ab sence of paralytogenic properties (in contrast to vaccines pre pared from nervous tissue) (2) a possibly higher immuno genic power of living virus vaccines and (3) possibility of longer duration of immunity in dogs vaccinated with living virus as compared with phenolized vaccines

[This finding may be an important advance both for veterinary and for clinical practice —Ed]

Use of Hyperimmune Antirabies Serum Concentrates in Experimental Rabies is reported by Hilary Koprowski James Van der Scheer and Jack Black[4] (Pearl River N Y) Rabies is the only known viral disease of man which is uniformly fatal Efforts to develop a protective treatment after expo sure have not gone much beyond the classic Pasteur proce dure and use of the original Pasteur vaccine or its modifica tions has been the main bulwark against rabies The consensus is that Pasteur s treatment is futile for persons so severely bitten by rabid animals that the incubation period is shorter than 30 days Furthermore evidence is overwhelming that Pasteur s treatment is associated with so called neuroparalytic accidents

The authors therefore attempted to develop if possible a substitute for or an adjunct to Pasteur s treatment Prelimi nary results with serum protection were sucessful because in screening laboratory animals hamsters were found ideally suited for this research

TECHNIC —Antirabies serum was obtained from rabbits or sheep hyperimmunized by replicate injections of egg adapted Flury strain and rabbit brain fixed viruses To test protective power of serum concentrates hamsters or guinea pigs were inoculated in tramuscularly with a suspension of canine salivary gland infected with the NYC strain of rabies virus Generally hyperimmune anti rabies serum was administered in a single subcutaneous injection of 1 ml /animal 24 hours after virus injection For comparative test of the protective power of serum and of phenolized vaccine prepara tions additional animals were treated each day for 14 consecutive days *with 0 5 ml of the respective* dilutions of vaccine the first injection usually being given 24 hours after virus inoculation

(4) Am J Med 8 412 420 Ap il 1950

serum neutralization technics and antibody response in chickens

A junior veterinary student did an autopsy on one chicken with a history and symptoms suggestive of acute Newcastle disease and on two such chickens the next day The following day his right eye became red and swollen and gross examination revealed edema of lids and hyperemia of scleral and conjunctival blood vessels Material obtained from a sterile swab placed in the medial canthus of the eye revealed the virus Virus identification was confirmed by hemagglutination hemagglutination inhibition and serum neutralization In addition virus sent to the Pathological Division U S Bureau of Animal Industry was identified as Newcastle virus

This is believed to be the first report of isolation of the virus of Newcastle disease from man in the United States

[These ocular infections are the only established instances of Newcastl virus disease in human being —Ed]

Nonspecific Heat Labile Factor in the Serum Neutralization Test for Newcastle Disease Virus is thought by Beatrice F Howitt[6] (U S Pub Health Service Atlanta Ga) to have caused false positive results and led falsely to the inference that Newcastle virus disease is common in humans

In 1948 it was reported that neutralizing antibodies against the Newcastle disease virus (NDV) of chickens had been found in serums of certain patients with either atypical neurologic symptoms (children) or an influenza like syndrome (adults) NDV was not recovered from either feces or nasal washings of any of these patients More excreta and more human serums were then tested Many serums showed high neutralization indexes In fact so many were positive that specificity of the tests was questioned Further doubt was manifested when serums of normal laboratory animals not in contact with the virus also gave definite protection against NDV

Because it was not the custom of the laboratory to inactivate serums for neutralization tests against neurotropic viruses all serums studied before this period had not been heated before use When the presence of a nonspecific heat labile factor was suspected experiments were run in duplicate

(6) J Immu 1 64 73 83 F bruary 1950

duplicate in hamsters the sequence of events occurring in man after a moderate or light exposure Therefore caution should be exercised before condemning Pasteur s treatment for human beings despite the lack of supporting experimental evidence in animals It is concluded that antiserum has definite value and should be applied in every case of exposure to rabies in conjunction with a short course of vaccine treatment

[These results are also encouraging and warrant further clinical trial —Ed.]

NEWCASTLE VIRUS DISEASE

Isolation of Virus of Newcastle Diseases from Human Beings Newcastle disease (avian pneumoencephalitis) is one of the more recent diseases affecting poultry in the United States In young birds it produces respiratory and nervous symptoms whereas in older birds symptoms are primarily respiratory The causative agent is a filtrable virus closely resembling human influenza virus A and B Although much has been written about Newcastle disease in poultry only six reports in the literature mention its occurrence in human beings W L Ingalls and Ann Mahoney[5] (Ohio State Univ) report recovery of the virus from apparently infected human beings in Ohio

A broiler plant operator brought several chickens to the Poultry Diagnostic Laboratory History and symptoms shown by the birds were indicative of Newcastle disease This was confirmed by isolation of the virus and hemagglutination inhibition technics It was noted that the flock owner had a definite conjunctivitis of the left eye He stated that the condition had been observed three days after sickness appeared in his flock and had been present for three days but was apparently improving Gross examination revealed edema of the lids pronounced hyperemia of the scleral and conjunctival vessels and a definite mucopurulent discharge No general symptoms had been noted Exudate recovered on a sterile cotton swab placed in the medial canthus of the affected eye was found to contain Newcastle virus Virus identification was confirmed by hemagglutination hemagglutination inhibition

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(5) Am J P b H lth 39 73 740 J 1949

meningoencephalitic symptoms may be more prominent and a cutaneous rash and icterus due to hepatitis frequently occurs Age appears to be important since infants show more severe and extensive lesions at autopsy than adults

Subacute toxoplasmosis designates cases in which there are regressing lesions in the extraneural viscera whereas in the central nervous system and the eyes toxoplasma continues to proliferate actively Most neonatal cases of toxoplasmosis fall into this group Disappearance of the organism from extraneural viscera can best be explained on the basis of acquired immunity Persistent proliferation of the organisms in the central nervous system may be explained by the observed poor diffusion of serum antibody into brain substance Symptomatic subacute toxoplasmosis frequently is fatal but surviving patients have been observed

Chronic toxoplasmosis refers to cases with clinical or laboratory evidence of toxoplasmosis but without signs of widespread activity Clinical signs and symptoms of past or persistent (chronic) toxoplasmosis may be variable according to the amount of damage produced during acute and subacute stage of the disease In symptomatic patients chorioretinitis is the most frequent sign followed in incidence by electroencephalographic evidence of cerebral damage cerebral calcifications demonstrable radiologically and other signs such as microcephaly hydrocephaly ocular malformations spastic paraplegia and their associated symptoms

In transplacental toxoplasmosis the question arises as to whether the mother s initial infection with toxoplasma was contracted during pregnancy or whether she had a chronic latent infection in the course of which a few organisms escaped from a ruptured pseudocyst infecting the placenta and hence the fetus Though either of these possibilities appears possible primary infection of the pregnant mother seems more likely to be the commoner mode of fetal toxoplasmic infection

Isolation of toxoplasma from a patient is the most significant single datum in establishment of diagnosis During the acute stage of infection organisms may be recovered from blood bone marrow splenic puncture material cerebrospinal fluid and possibly sputum During subacute stages organisms

on both heated and unheated material In every instance in which the unheated specimen gave a high titer an inactivated specimen of the same serum gave negative results Further experiments were undertaken to evaluate the nature of the neutralization tests against NDV when using human serums and to determine whether previous results with unheated serums were of any significance

From these studies it was concluded that previously published positive results were due to a nonspecific heat labile factor in the serums Heating to 56 C for 30 minutes completely destroyed virucidal activity of all serums except those from specifically immunized animals This virucidal factor for NDV was found in large amounts in the normal serum of man monkey rabbit and guinea pig in correlation with the hemolytic activity of the complement It may possibly be associated quantitatively with one of the four components of complement

[The author has very properly corrected some previously published work which indicated that Newcastle disease was fairly common in human beings —Ed]

TOXOPLASMOSIS

Pathogenesis, Diagnosis and Treatment of Human Toxoplasmosis are discussed by J K Frenkel[7] (Hamilton Mont) In human beings a number of clinical forms of toxoplasmosis have been recognized characterized chiefly by (1) congenital or neonatal meningoencephalitis usually associated with hydrocephaly chorioretinitis cerebral calcifications and convulsions (2) atypical encephalitis (3) postencephalitis sequelae or (4) pneumonitis associated with fever and rash The causative organism Toxoplasma gondii is generally believed to be a protozoan

Acute toxoplasmosis is a generalized infection involving every organ although lesions may be only microscopic Toxoplasma has been observed to proliferate intracellularly in many types of cells Most frequently encountered involvements are interstitial pneumonitis myocarditis encephalitis splenitis hepatitis and orchitis Clinically pulmonary or

(7) J A M A 140 369 377 May 28 1949

course of these lesions cannot be predicted any improvement occurring during treatment cannot necessarily be said to be due to it

Serologic Diagnosis of Human Toxoplasmosis Toxoplasma an intracellular protozoon parasite was identified in 1909 but only within the last 10 years has it been shown to cause human disease Apart from its exceptionally wide host range little is known about the biology of the parasite or about the epidemiology and incidence of human infections Toxoplasmosis in overt or symptomless form may occur at any age but most recognized cases have been in infants with congenital abnormalities Hydrocephalus chorioretinitis and cerebral calcification are characteristic signs in infants but diagnosis can be made with assurance only by infecting animals from human tissues by recognizing the protozoon in histologic section or by serologic methods The parasites have rarely been recovered from patients during life and histologic sections are usually available only after death Serologic tests have been devised and used extensively but are technically complicated The complement fixation method appears to be more suitable



Fig 10—Toxoplasma in chorioallantois (Courtesy of M do ld 4 Lancet 1 950 953 J 4 1949)

Alexander Macdonald[8] (Univ of Liverpool) made tests for a simple laboratory method of recognizing toxoplasma infection Two technics were used both designed to detect antibody in human serum a neutralization test on chorioallantois of the developing hen s egg and the complement fixation test with antigen prepared from infected chorioallantoic membranes (Fig 10) Tests on four positive human serums one immune rabbit serum and over 60 normal serums indicated that both methods give reliable results

[This appears to be a simpler procedure than previous diagnostic tests for toxoplasmosis —Ed]

(8) Lancet 1 950 953 June 4 1949

have been found in ventricular fluid obtained by aspiration and from the central nervous system at autopsy In the chronic state organisms may be present in the central nervous system eye and myocardium They are easily recognizable in sections stained with hematoxylin and eosin or with one of the polychromic methylene blue dyes During acute infection biopsy specimens of skin lymph node bone marrow liver and spleen may be available Ventricular fluid sediment may be obtained from patients in subacute stages and treated like a button A cutaneous test with toxoplasma antigen (toxoplasmin) is the most useful simple aid in diagnosis of past or latent toxoplasmosis whenever isolation of the causative organism is not feasible The diagnostic antigen is derived from sediment of mouse peritoneal fluids rich in toxoplasma The toxoplasma netralizing antibody test has proved useful in demonstrating such antibodies as may be found in subacute and chronic state of the infection

Sulfadiazine and sulfamerazine in full doses has been observed to control acute toxoplasmosis in animals and the successful treatment of a child with predominantly meningoencephalitic signs and symptoms has been reported Treatment should be continuous for about two to three weeks until sufficient immunity has been acquired to prevent relapse In subacute toxoplasmosis extensive mechanical and usually irreversible lesions are present by the time diagnosis is made Although treatment with sulfonamides has proved effective in suppressing proliferation of organisms such treatment does not appear to be promising In chronic active toxoplasmosis lesions are thought to be due to rupture of toxoplasma pseudocysts giving rise to localized reactions of hypersensitivity Consideration of this concept has led to attempts at desensitization of patients with active chorioretinitis and evidence of toxoplasmic infection by cutaneous and serologic tests So far nine such patients have been treated by injection of graded increasing doses of toxoplasma antigen supplemented in some instances by nonspecific protein therapy with intravenous administration of typhoid vaccine Lesions became inactive during treatment in eight patients as indicated by disappearance of vitreous exudate decreased retinal edema and infiltration and beginning pigment deposition Since the

course of these lesions cannot be predicted any improvement occurring during treatment cannot necessarily be said to be due to it

Serologic Diagnosis of Human Toxoplasmosis Toxoplasma an intracellular protozoon parasite was identified in 1909 but only within the last 10 years has it been shown to cause human disease Apart from its exceptionally wide host range little is known about the biology of the parasite or about the epidemiology and incidence of human infections Toxoplasmosis in overt or symptomless form may occur at any age but most recognized cases have been in infants with congenital abnormalities Hydrocephalus chorioretinitis and cerebral calcification are characteristic signs in infants but diagnosis can be made with assurance only by infecting animals from human tissues by recognizing the protozoon in histologic section or by serologic methods The parasites have rarely been recovered from patients during life and histologic sections are usually available only after death Serologic tests have been devised and used extensively but are technically complicated The complement fixation method appears to be more suitable



Fig 10—Toxoplasma l on on ho o- ll ntois. (Cou t y f Macdonald A Lancet 1 950 953 J n 4 1949)

Alexander Macdonald[8] (Univ of Liverpool) made tests for a simple laboratory method of recognizing toxoplasma infection Two technics were used both designed to detect antibody in human serum a neutralization test on chorioallantois of the developing hen s egg and the complement fixation test with antigen prepared from infected chorioallantoic membranes (Fig 10) Tests on four positive human serums one immune rabbit serum and over 60 normal serums indicated that both methods give reliable results

[This appears to be a simpler procedure than previous diagnostic tests for toxoplasmosis —Ed.]

(8) La t 1 950 953 J ne 4 1949

Meningoencephalitis Due to Trichinella Spiralis is reported by Michael S Bruno and Maurice Goodgold[9] (New York Univ) The case follows

Youth 16 was hospitalized because of an illness of eight days duration and characterized by puffiness of eyes fever up to 105 F severe headache and generalized malaise Physical examination revealed a moderately injected throat and striking conjunctival injection He was given combined sulfonamide and sulfathiazole therapy and later penicillin On the sixth day he became disoriented and developed visual hallucinations A Babinski sign was found on the right He was therefore transferred to Bellevue Hospital

On admission examination revealed a temperature of 104 6 F pulse 120 respirations 30 and blood pressure 90/60 He was weak and appeared to be in some respiratory distress Eyelids were puffy Neck was definitely supple Neurologic examination revealed absence of all deep tendon reflexes except for those of the arms which were hypoactive Abdominal and cremasteric reflexes were also absent Bilateral Babinski signs were noted Red cell count was 4 490 000 and white cell count was 13 400 with 73 per cent neutrophils 21 per cent lymphocytes 3 per cent monocytes 2 per cent eosinophils and 1 per cent basophils Cerebrospinal fluid was normal

During the next few days the patient became worse Nuchal rigidity was evident and Kernig s and Brudzinski s signs were demonstrated However a second spinal tap again revealed normal cerebrospinal fluid On the ninth day the patient complained of severe generalized muscle pain and tenderness for the first time A trichinella precipitin test was positive with an antigen dilution of 1 1,280 and 13 per cent eosinophilia was found

The patient became asymptomatic by the 21st hospital day when 18 per cent eosinophilia was noted This gradually rose in the next two weeks to 56 per cent Biopsy of the left gastrocnemius muscle on the 32d day revealed trichinella

On close questioning the patient denied eating pork immediately before onset of illness However he remembered eating frankfurters five days before onset

Trichinosis begins when uncooked undercooked or under processed pork containing encysted trichinella larvae is ingested Meat fibers and capsules containing the parasites are digested liberating the larvae in the gastrointestinal tract Larvae attach themselves to the mucosa and burrow into the crypts of the small intestine in which they mature rapidly

(9) New Y rk State J M d 50 707 710 M 15 1950

After copulation the viviparous gravid female gives birth to motile minute larvae which are deposited directly into intestinal lymphatics During this phase of the cycle the patient may develop many complaints referable to the gastrointestinal tract Larvae invade the intestinal lymphatics and enter the venous circulation While the larvae are migrating through pulmonary capillaries pneumonitis of varying severity may be produced Once they are in arterial blood trichinae are rapidly disseminated It is during this phase that the brain meninges and myocardium may become involved After a variable period the larvae having special predilection for skeletal muscle eventually concentrate and encyst there During this phase symptomatology referable to the musculoskeletal system is frequently elicited

[The manifestations of trichinosis depend on the chance deposit of larvae in any organ hence the variable clinical picture Eosinophilia, leukocytosis and orbital edema are the signs most likely to suggest the diagnosis —Ed]

COLLAGEN DISEASES

Disseminate Lupus Erythematosus Hamilton Montgomery (Mayo Clinic) and William G McCreight[1] (Mayo Found) present an analysis of 132 cases of disseminate lupus erythematosus seen from 1938 through 1947 The predominance of women in this series (83 per cent of 23 patients with chronic 87 per cent of 77 with subacute and 91 per cent of 32 with acute cases) fits in with reports of series elsewhere in which as high as 95 per cent of cases has been in women

Diagnosis of lupus erythematosus without cutaneous manifestations is difficult All patients in this series presented evidence of cutaneous lesions at some time during the disease However in four additional patients seen during the period of this study a diagnosis of disseminate lupus erythematosus seemed justifiable despite absence of cutaneous lesions as lupus erythematosus cells were found in the sternal marrow of three There can be no question that bona fide cases of lupus without cutaneous lesions have been reported

(1) A h D mat & Syph 60 356 372 Septembe 1949

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(9) New York State J M d 50 707 710 M 15 1950

multiple factors The authors believe that the concept of tuberculous origin should be abandoned After review of cases of various types associated with pregnancy they believe that pregnancy may at the most be merely a contributing factor and that therapeutic castration of women with disseminate lupus is valueless Allergic factors did not predominate in any of the authors patients Studies of histologic changes in the skin in various types of disseminate lupus erythematosus showed only minor changes in collagen or fibrinoid degeneration in the walls of vessels The authors prefer therefore not to regard the condition primarily as a collagen disease but to continue to regard the cause as unknown

Diagnosis should be considered even without cutaneous lesions when several of the following combinations or signs occur arthralgias or arthritis cardiac symptoms evidence of renal irritation or nephritis associated with malaise a septic type of temperature leukopenia and secondary anemia an increased sedimentation rate false positive reactions in Wassermann and flocculation tests albumin erythrocytes and at times casts in the urine and reversal of the albumin globulin ratio To this group may be added tentatively demonstration of so called lupus erythematosus cells on sternal aspiration False positive reactions in Wassermann or flocculation tests occur in increasing percentage according to the acuteness of the disease as do also increased sedimentation rates and reversal of the albumin globulin ratio

Clinical Course of Disseminated Lupus Erythematosus Evaluation of Osler s Contributions After analysis of 32 cases of lupus erythematosus seen in recent years in all of which diagnosis was proved by pathologic examination Philip A Tumulty and A McGehee Harvey[2] conclude that Osler constructed a framework for the clinical picture of this disease and that others have supplied details There seems to be little or nothing of real significance as far as clinical manifestations are concerned which he omitted Frequency distribution of the various features which he emphasized remains essentially the same He focused attention on those features of the disease which as review of these 32 cases made obvious are still of paramount importance

(2) Bull Johns Hopkins Hosp 85 4 73 July 1949

in the literature with or without their having had the features of the Libman Sacks syndrome

Aspiration of sternal marrow was attempted in 26 patients 7 of whom were classified as having acute disseminate lupus erythematosus The marrow of five of these was positive for lupus erythematosus cells and that of one was suggestive In one the attempt at aspiration was unsuccessful The five patients with lupus cells and the one with cells resembling lupus cells are known to have died Eighteen of the 26 patients had subacute disseminate lupus erythematosus The marrow of 12 was negative of 3 positive and of 1 suggestive Sternal marrow in one case of chronic disseminate lupus erythematosus was negative Lupus erythematosus cells appear to predominate in cases of disseminate lupus erythematosus in which the disease is active or increasing and are usually not demonstrable if the condition is quiescent Lupus cells have not been reported in any other condition except one case of multiple myeloma Further observations of a large series however are necessary for their status and diagnostic significance to be determined

Analysis of various systemic manifestations in the present series showed no fundamental variations from those reported previously However several patients presented symptoms which involved the central nervous system and which were not terminal manifestations but were encountered early in acute or subacute disseminate lupus erythematosus Symptoms in one patient included headaches choked disks and palsy of the face with evidence at autopsy of endarteritis of cerebral vessels Another patient a girl 16 had cerebro thrombosis convulsions aphasia and weakness in addition to evidence of anemia increased sedimentation rate renal irritation and false positive serologic reactions Another patient had nervous irritability and a cerebral accident with convulsions and euphoria when seen a year later she had typical lesions of lupus of the scalp and body and aspirated bone marrow was positive for lupus erythematosus cells Although the tendency has been to focus attention on cardiac renal hepatic splenic or arthritic involvement in lupus erythematosus it is evident that any organ in the body may be involved

Disseminate lupus erythematosus has been attributed to

intramuscularly in four divided doses Before treatment was begun patients with disseminated lupus were tested for response of the adrenal cortex to stimulation by adrenocorticotropic hormone Intramuscular injection of 50 mg promptly elicited a normal response in each case as evidenced by significant drop in circulating eosinophils and by increased urinary excretion of neutral 17 ketosteroids and 11 oxygenated steroids

These severely ill patients responded to adequate cortisone or ACTH therapy within 48 hours with a feeling of well being improved strength and amelioration of arthralgia Temperature usually returned to normal by the fourth day of therapy gallop rhythm and tachypnea if present subsided mouth lesions healed pain and swelling of joints disappeared and any pleuritis and pericarditis rapidly vanished In 10 days after beginning of adequate therapy the characteristic erythema disappeared except perhaps for some residual pigmentation of previously affected areas and the patients appeared on the road to convalescence

After disease had been arrested by cortisone and patients seemed clinically well usually after two or more weeks of therapy at maximal doses the amount was gradually reduced every three or four days until a maintenance level was determined Daily maintenance dose required to hold the gain was between 50 and 100 mg Reduction below that amount usually resulted in three or four days in recrudescence of fever and return of other symptoms and signs Complete withdrawal of the drug resulted in a few days in prompt recurrence of disease so that it was necessary to reinstitute therapy in full doses to prevent jeopardizing life

These experiences led to substitution of ACTH for cortisone as soon as minimal maintenance requirement for cortisone had been determined It was felt that continued use of large doses of cortisone had partially suppressed adrenal cortical function and therefore after disease had been controlled clinically by cortisone the patients required reactivation of adrenal cortical function by ACTH stimulation if relapse was to be prevented By replacing maintenance dose of cortisone with an equivalent amount of ACTH (75 100 mg daily in four divided doses for four or five days) the daily amount

The cutaneous lesions have visceral counterparts which may occur in the absence of any dermal abnormalities Although the disease may manifest itself through alterations in any of the organ systems cutaneous joint and renal manifestations are most prominent Osler noted that the endocardium was at times involved and reported hemorrhagic manifestations He emphasized that the disease may have a protracted course during which varied clinical abnormalities appear rendering diagnosis difficult unless one has the opportunity to follow the illness over a long period Osler realized the kinship of the diseases of the rheumatic group but pointed out the possibility of different etiologies This thought finds later expression in the belief of certain investigators that these are clinical entities of varying etiology involving primarily the same system of the body thus they assume an outward similarity though etiologically distinct

Just as certain features of Osler s cases were particularly striking in the present group nervous system involvement similarity of joint lesions to those of rheumatoid arthritis incidence of thrombocytopenic purpura and the frequency with which secondary infections occurred were striking The difficulty of recognizing these complications in a disease with such widespread lesions is obvious Equally obvious is the importance of their recognition in the presence of a disease which may run a relatively benign course for many years

The authors conclude that their review has added nothing new to the fundamental expressions of Osler but serves as an echo of his clinical genius

Treatment of Disseminated Lupus Erythematosus with Cortisone and Adrenocorticotrophin George Baehr and Louis J Soffer[3] (Mount Sinai Hosp New York City) report their observations on treatment of nine patients with various forms of collagen disease five of whom had disseminated lupus erythematosus Of the five four were females and one was a boy aged 13 Only patients who appeared to be on the verge of death were selected for therapy because the drugs were scarce Required daily therapeutic dose of cortisone for severe cases of long standing proved to be 150 200 mg daily in four divided doses of ACTH about 100 mg daily also administered

(3) B ll New Y k A d Med 26 29 234 Ap 1 1950

F g 11—P t t w th scl o- d rm *A* th d y bef e begin n g f p m b cid the py *B* 34 day ft begi g f t tm t. Loo g f th kin pp ent pe lly t th b t f ld *C* 34 d y ft beg ng f t tm t pa t w bl to se her rm ove head d to sm l b oadly (C t y f Z f t C J D *et* *l* A b Int. M d 85 27 43 J y 1950)

was gradually reduced during the succeeding four to six weeks until the patient s own adrenals had assumed the full load Thus patients were slowly weaned of the need for ACTH

Though treated patients lost all manifestations of the dis ease and appeared to have recovered clinically their illness must be regarded as only in remission In all patients leuko penia persisted erythrocyte sedimentation rate remained ac celerated and L E cells were still found in heparinized bone marrow and in buffy coat of heparinized blood Recurrences are anticipated

Serious hazards accompany administration of these hor monal preparations Within a week of onset of therapy weight gain was sometimes rapid due to increase in body water and to associated disturbances in distribution of blood electrolytes Simultaneously both systolic and diastolic blood pressures often rose This combination of events may induce heart failure As in Cushing s disease shift in blood electro lytes to cells may result in alkalosis Use of mercurial diuret ics to combat congestive heart failure may accentuate this tendency In one patient carbon dioxide combining power of blood plasma rose to 102 volumes per cent during therapy blood chlorides dropped to 79 m Eq /L and serum potassium dropped to 1 9 m Eq /L It became necessary to administer hypertonic potassium chloride intravenously to correct alka losis and threatening hypopotassemia either of which could have been fatal Cerebral disturbances were encountered in two patients being treated

[This is a useful account of a comparatively large experience in ther apy of lupus erythematosus with these new agents As mentioned in the final paragraph the therapy may lead to very serious side effects —Ed]

Use of Para Aminobenzoic Acid in Dermatomyositis and Scleroderma Report of Six Cases is made by C J D Zarafonetis A C Curtis and A E Gulick[4] (Univ of Michigan) The rationale for administering large doses of para amino benzoic acid (PABA) to patients with lupus erythematosus is as follows Exposure to sunlight may induce a relapse or cause an exacerbation of lupus erythematosus Manifestations of sensitivity to sunlight have also been encountered in per sons receiving sulfonamide compounds Since PABA and sul

(4) A h I t Med 85 7-43 J n y 1950

tol) points out that this disorder occurs in all age groups Except when there is coexistent asthma children with polyarteritis have rarely been found to have eosinophilia Clinical signs of the disease in 44 children were purpuric rash 34 per cent other rashes including urticarious 27 per cent and palpable nodules 4 5 per cent The cutaneous form of arteritis



F g 12—I hem c ff ct fi g n fi al cut ph se f nerr t g ol l te t e t it (Court y f N l A V A h D Ch ldhood 24 2 4 229 sept m ber 1949)

is particularly di tinguished by the occurrence of painful nodular swellings in the skin which are both visible and palpable Two cases follow

CA E 1—Girl 9 was hospitalized with a history of recent streptococcic tonsillitis followed by rheumatic pains and an unusual skin rash. The two outstanding visible signs were a persistent flexural position of the limbs in bed and a decided mottled rash all over the body e pecially on the limbs The ra h was similar to that of cadaveric staining and varied in intensity from day to day Fluctuating appearance of subcutaneous tender nodules indicated that ubcutan ous arteries were affected by acute focal nodular and inflammatory changes Repeated examination reveal d no renal or cardiac involvement For eight months there was undulating pyrexia with persistent leukocytosis but eosinophil were never more than

fonamides are metabolite antagonists it was reasoned that the former might be beneficial in lupus erythematosus Accordingly clinical trial was undertaken in 18 patients

During this study a patient with dermatomyositis observed that exposure to sunlight made the cutaneous eruption more uncomfortable and she was rapidly becoming worse despite empiric measures Therefore it was deemed justifiable to treat the patient with PABA The results were favorable so five other patients were similarly treated In all six cases sodium para aminobenzoate was administered in doses of 18 24 Gm daily (taken in 2 or 3 Gm doses at two or three hour intervals) for periods varying from weeks to months Two patients one with classical dermatomyositis and one with features of both dermatomyositis and scleroderma improved greatly during prolonged therapy Three of four patients with scleroderma also had beneficial effects

The question arose whether improvement could be attributed to the administration of PABA salts One patient was experiencing rapid progression of the disease process at the time PABA therapy was begun improvement was noted within a few days The possibility that this may have been due to spontaneous remission was considered however the patient gave a history of relapse when she discontinued PABA therapy at home and resumption of therapy was again accompanied with improvement which was maintained Furthermore biopsy specimens of muscle revealed the presence of active myositis after some 10 months of treatment This suggested that there had been neither a cure nor a spontaneous remission but that PABA compounds had somehow suppressed the dermatomyositis

The mechanism of action of PABA in dermatomyositis and scleroderma is obscure as it is in lupus erythematosus It is possible that the effect of PABA in these diffuse collagen diseases is supportive evidence of a close relationship among them Additional investigation of the use of PABA in these conditions is warranted

[Para aminobenzoic acid therapy is comparatively harmless and worth trying but our experience with it has been disappointing —Ed]

Polyarteritis in Childhood A V *Neale*[5] (*Univ of Bris*

(5) Arch D Childhood 4 429 September 1949

ations In three cases nodules of choroiditis were found soon progressing to scar formation In one case retinal arteries were directly affected by the polyarteritic process and it was possible to observe the typical sequence of arteritis obstruction of the lumen aneurysmal dilatation and scar formation In two cases the choroidal nature of the ophthalmoscopic picture became obscured and almost obliterated by retinal changes associated with malignant hypertension which are the ocular signs most commonly described in recorded cases of polyarteritis nodosa

Though nodules of choroiditis and retinal detachments occur in other diseases their rapid onset and retrogression and changing location over the fundi are features which appear to be characteristic of polyarteritis nodosa Their clinical course is more suggestive than their presence and close observation over weeks is necessary

Until fundi are thoroughly examined with the pupil dilated in a sufficiently large series of cases frequency of ocular signs of direct vascular involvement cannot be estimated In most recorded cases of polyarteritis nodosa there is only passing reference if that to the eyes This may be due to the comparative mildness of symptoms produced by such gross eye lesions amounting in the cases reported to no more than slight mistiness of vision However these eye changes were observed in four of six or seven cases seen by the authors within the last three years Prognostic significance of ocular findings appears to be grave Average duration of life in these four cases was just over six weeks after discovery of the first eye signs

It is helpful to contrast eye changes in polyarteritis nodosa with those in temporal arteritis in which the common lesion is occlusion of the central retinal artery No choroidal damage retinal detachment or aneurysms have been recorded in temporal arteritis and the ocular involvement seems to have no bearing on prognosis which is usually favorable as regards life The relative frequency of choroidal lesions in polyarteritis nodosa is due probably to the predilection of the disease for vessels of medium size and to the fact that there is a greater number of such vessels in the choroid than in the retina

4 per cent Blood cultures were negative Biopsy revealed prolifera tion of subendothelial connective tissues of the intima and of va cu lar granulation tissues of the media with much disarrangement of muscle fibers in most arteries in the subcutaneous tissue and in a lesser degree in those of the cutis vera There were necrobiotic changes of the media After a prolonged hospital stay gradual im provement occurred In the following two years periarterial nodules occasionally appeared usually accompanied by limb pains Several days of immobility would follow At age 13 clinical recovery was complete

CASE 2—Boy 8 was hospitalized because of generalized macu lar rash numerous red purple focal swellings and joint pains which had appeared three days after he had been given a sulfonamide for a sore throat Histologic examination of a subcutaneous nodule confirmed the diagnosis of periarteritis nodosa Blood studies showed a fluctuating neutrophilic leukocytosis but eosinophils never ex ceeded 1 5 per cent Temporary joint swellings with small effusions appeared Clinical examination and electrocardiograms revealed a normal heart Variable pyrexia continued for many weeks Eventu ally the patient became ambulatory and comfortable but a few cutaneous arterial nodules appeared at intervals and cadaveric staining on the limbs was persistent Some 18 months after onset he had a cold recurrence of limb pains and decided accentuation of cutaneous erythema His condition quickly deteriorated and pro gressed to acute obliterative cutaneous arteritis and spreading ischemic necrosis (Fig 12) Autopsy revealed no evidence of visceral involvement

Ocular Manifestations of Polyarteritis Nodosa R N Her son and R Sampson[6] point out that though wider knowledge of the main clinical features of polyarteritis nodosa is ena bling correct diagnosis to be made during life with increasing frequency the disease is protean and many difficulties arise Little attention has been given to the help which may be ob tained by careful and repeated examination of the fundus of the eye

In four cases reviewed by the authors ophthalmoscopic signs began with blurring of the edges of the disk and one or two small hemorrhages adjacent to it Soon afterward wide areas of retinal edema appeared and retinal detachments of various sizes occurred which tended to recover spontaneously sometimes in less than two weeks The fluctuating nature of these exudative detachments can be correlated with the known transient nature of the localized areas of edema in other situ

(6) Q rt J Med 18 1 313 Ap 1 1949

No significant difference was found in incidence of infected foci in the upper respiratory tract of patients with rheumatoid arthritis compared with the controls Results do not suggest that infections of the ear nose or throat play an important part in etiology of this disease

[There is no justification for removal of teeth and tonsils in a patient with rheumatoid arthritis except on the basis of the local disease Fortunately the remove all foci of infection doctrine is going out of style —Ed]

COMPLICATIONS OF VACCINE INJECTIONS

Local Paralysis in Children after Injections J K Martin[8] (Guy s Hosp London) draws attention to the association between intramuscular injections and flaccid paralysis of one limb He has personally studied 17 affected children and has examined records of 60 70 additional cases

Age groups of these children reflected average age at which immunization is carried out Average time between injection and onset of paralysis was 16 days the range being 3 26 days Without exception constitutional disturbances either preceded or occurred at time of onset of paralysis Nine patients had a history of fretfulness lethargy anorexia or pyrexia within one to four days of paralysis In eight children an upper respiratory infection pyrexia or fretfulness occurred at some time following inoculation Neck rigidity was found in four and pyrexia in five patients seen at time of onset Pain and tenderness were never apparent but since all children were aged less than 3 years this did not entirely exclude their presence Onset of paralysis was sudden with a flaccid paralysis of the whole limb as a rule The left arm was paralyzed four times as frequently as the right presumably because the left deltoid muscle is the commonest site of inoculation Cranial nerves were not involved and in only two patients was any paralysis noted other than in the involved limb and then it was only transient Sensation appeared normal Distribution of paralysis corresponded to muscles supplied by motor roots of the fifth sixth and seventh cervical segments of the spinal cord Corresponding tendon reflexes were absent Cerebrospinal fluid was examined in seven cases

(8) A h D s Ch ldhood 25 1 14 M h 1950

Focal Infection in Rheumatoid Arthritis Comparison of Incidence of Foci of Infections in Upper Respiratory Tract in 100 Cases of Rheumatoid Arthritis and 100 Controls was made by L S P Davidson J J R Duthie and Max Sugar[7] (Univ of Edinburgh) Since no data were obtainable regarding the incidence of focal infection in patients with rheumatoid arthritis compared with suitable controls examined under similar conditions it was thought that such a study might be of considerable value in reaching a decision as to the importance of eradicating foci of infection when treating this disease Furthermore little information is available on the incidence of foci of infection in healthy people and in patients suffering from diseases other than rheumatoid arthritis

Foci of infection are frequently found in patients with rheumatoid arthritis but their etiologic significance is obscure Many now believe that a focus of infection is the means whereby tissues become sensitized to bacterial antigens and that an abnormal immunologic response follows any further contact with the original antigen Because no satisfactory proof exists that such a sensitizing mechanism is the essential factor underlying development of rheumatoid arthritis an attempt was made to determine if a significantly higher incidence of focal infection is present in patients with rheumatoid arthritis than in a comparable group of controls

Because ear nose and throat infections are more prevalent at certain seasons examination of the 100 patients and 100 controls was spread throughout one entire year so that both groups would be equally affected by seasonal variations Controls of comparable age and sex were selected primarily from patients in whom diagnosis of rheumatoid arthritis could be excluded There were 29 males and 71 females in each group All patients were given an ear nose and throat examination without reference to presence or absence of rheumatoid arthritis The presence of a septic focus was decided solely by careful examination of the upper respiratory tract X rays of sinuses were made but proof puncture was not performed when opacity was *demonstrated In absence of confirmatory* evidence obtained by washout these patients can only be regarded as having a possible sinus infection since opacity may be due to causes other than chronic infection

(7) A Rh m t D s 8 05 08 S ptembe 1949

vaccination have been reported for generations and have included urticarial and erythematous rashes generalized vaccinia local ulceration lymph node abscesses gangrene tetanus nephritis purpura encephalitis myelitis and peripheral neuritis It is with the last mentioned entity that this article is concerned Whereas there have probably been over 700 reported cases of postvaccinal encephalitis there are but 7 reported cases of postvaccinal neuritis Because of the rarity of the condition its striking clinical picture and its good prognosis and because the reported cases were not recognized by the referring physicians N William Winkelman Jr[9] (Philadelphia) describes five cases of disturbances of peripheral nerves and roots which occurred as a result of the mass smallpox vaccination program in New York City during three weeks in March and April 1947 when approximately 6 350 000 persons were immunized

Analysis of the five cases reveals that in all the reaction followed revaccination for smallpox Site of inoculation was in the deltoid region Site of involvement was independent of the area of inoculation Incubation period varied from 7 to 14 days Onset was hyperacute with severe sharp pain in the shoulder in four cases and paresthesias in one All patients showed decided weakness after one to four days Systemic complaints were mild or absent Weakness subsided after several weeks All had muscle tenderness decreased tone decreased to absent deep reflexes atrophy and paresis Four had objective and all had subjective sensory disturbances Spinal fluid protein was normal in four patients and somewhat elevated in one Results of other laboratory studies were essentially normal All had practically total clinical recovery in four months Sensory improvement began much earlier than motor improvement and tended to be more nearly complete A history of vaccination against smallpox 7 14 days before onset of symptoms was the most important diagnostic point

Winkelman concludes that postvaccinal disturbances of both peripheral nerves and of roots are rare and occur after a relatively constant incubation period The clinical picture is typical and prognosis good There may be motor sensory or mixed involvement Sensory disturbance initiates the disease

(9) A h Neu l & P y h t 62 4 1438 O t b r 1949

Changes found included an elevated cell count and serum protein level and were consistent with those found in poliomyelitis

Treatment similar to that for poliomyelitis was used Paralyzed muscles were splinted and arms were put in an airplane abduction splint The most important part of physical treatment was to remove all splinting at least twice daily and put the joints through a full range of motion Approximately 50 per cent of patients made a good functional recovery

There appeared to be no relation between inoculation substance and paralysis Materials used included alum precipitated toxoid pertussis vaccine alone or combined albumose free tuberculin and penicillin Material used was produced by *at least six different manufacturers*

There was suggestive evidence that these cases occur chiefly when there is a high prevalence of poliomyelitis Maximal seasonal incidence was in summer and autumn months with sporadic cases practically throughout the year Just over 50 per cent of all known cases occurred between July and September and about 30 per cent in October to December This seasonal incidence closely parallels that of poliomyelitis

Diagnosis in almost every case was poliomyelitis In general no inquiry as to recent inoculations or injections was made until a later date The question remains whether the *relation between an inoculation and subsequent paralysis is* fortuitous True incidence of such an association is difficult to obtain Study of two sets of poliomyelitis records revealed that in one series of 80 cases there were 3 in which paralysis of one limb occurred within a month of inoculation In the other series of 56 7 such cases were discovered Despite the fact that relationship between inoculation and subsequent paralysis has not been proved statistically the association appears to be sufficiently important to suggest prophylactic measures If the public comes to associate inoculation with possible risk of paralysis immunization may thereby fall into disrepute *In view of this possibility* and the seasonal incidence it might be wise to suspend inoculations during part of the year or in areas where poliomyelitis is prevalent

Peripheral Nerve and Root Disturbances Following Vaccination against Smallpox The complications of smallpox

of homologous serum jaundice believed to have been transmitted by a tattooing needle None of the patients had a history of contact with clinical jaundice and none had been inoculated or subjected to venipuncture more recently than eight months before onset of symptoms It seemed highly improbable that a small outbreak of infectious hepatitis would be limited to a group of persons all of whom were tattooed on the same day in the same establishment several months previously Incubation periods of 126 132 139 and 144 days were consistent with a diagnosis of homologous serum jaundice It was thought most likely that the tattooing needle was contaminated with blood or serum of a customer who was either incubating serum hepatitis or suffering from a mild attack of the disease It is suggested that health authorities closely supervise tattooing shops and close those regarded as unsanitary

Two Simultaneous Cases of Leprosy Developing in Tattoos are reported by Ross J Porritt and Richard E Olsen[3] (St Joseph s Mercy Hosp Pontiac Mich) Two men from the same community while serving in the Marine Corps were tattooed by the same man on the same day in June 1943 in Melbourne Australia In both maculoanesthetic or tuberculoid leprosy developed in the tattoos during the first half of 1946 One man had many tattoos but leprosy developed only in the one done in Melbourne on the same day his friend was tattooed A third Marine tattooed at the same place but not on the same day has no evidence of leprosy These two cases provide strong evidence for spread of leprosy by inoculation

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DISEASES OF UNCERTAIN ETIOLOGY

Isolation from Cases of Infantile Diarrhea of Filtrable Agent Causing Diarrhea in Calves Many species of bacteria have been shown to have the capacity to produce diarrhea with regularity in animals or man Until comparatively recently however evidence for a possible virus etiology of diseases characterized chiefly by diarrhea has been scanty Jacob

(3) Am J P th 23 805 817 S pt mb 1947

producing marked distress and causes the patient to seek medical advice This is rapidly followed by motor impairment which tends to be more extensive and longer lasting than sensory Efficient physical therapy must be carried out to prevent sequelae

It is thought that the postvaccinal disturbances of peripheral nerves and roots belong in the same group as the serum neuritides The postvaccinal neuritides seem also to be related to neuritides associated with sulfonamide and penicillin therapy and perhaps with periarteritis nodosa in all of which allergy plays an important role

Damage to Visual Organs Resulting from Typhoid Inoculations Tore Kornerup[1] (Stockholm) performed ophthalmologic examinations on 26 patients with generalized neurologic symptoms which followed typhoid inoculation Of these 25 had symptoms relating to the eye In 15 of the 25 complaining of visual difficulties no other cause except the previous inoculation could be found In 10 patients ocular signs of disease were probably connected with the inoculation and included optic neuritis or neuroretinitis in 4 reversible impairment of color vision in 4 optic atrophy in 1 and fourth nerve palsy in 1

Cause of these complications is unknown It is possible that a latent virus disease of the nervous system becomes active after the typhoid inoculation In some cases an allergic *reaction to antityphoid serum seems likely The complications* reported are rare and have good prognosis Because long standing debility occasionally results from typhoid inoculation however persons with renal disorders or with luetic or other chronic inflammatory disease of the eye should not be inoculated even if these diseases appear to be cured The usual series of three injections should be discontinued if after the first injection the inoculated person has visual symptoms

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COMPLICATIONS OF TATTOOING

Homologous Serum Jaundice Transmitted by Tattooing Needle R H Roberts and Hereford Still[2] report four cases

(1) Acta ophth 27 383 391 1949
(2) Ca ad M A J 62 75 78 J ry 1950

displayed no immunity as typical disease developed One experiment was carried out by submerging filtrate in sealed containers in boiling water in a water bath for five minutes The agent was apparently not inactivated typical diarrheal disease developed in the calf receiving this material and injection with infectious material after recovery showed it to be immune Two experiments were made with filtrate maintained at 70 C for an hour this heating apparently failed to inactivate the agent Of two calves given material maintained at 80 C for one hour one remained well and later showed no immunity to the disease and in the other a modified form of the disease developed These data indicate that in one instance the agent had been inactivated by heating at 80 C for one hour and that in the other it had been attenuated

The disease studied in the six outbreaks appeared to be a single clinical entity Features common to all were a high morbidity rate absence of known pathogenic bacteria as causative agents and limitation of obvious symptoms of disease to infants under age 6 weeks The disease appeared regularly in both breast fed and artificially fed infants and premature infants seemed more susceptible than full term infants Because of these characteristics the authors believe they were dealing with outbreaks of epidemic diarrhea of the newborn

Additional evidence that the virus described was the cause of the disease in these infants was furnished by neutralization tests on serums from four infants who had recovered from the epidemic diarrhea Serums of two completely protected two calves against infection with the virus whereas those of two others showed partial protection The virus was not found in stools of any of eight normal newborn infants or five normal calves

[A filtrable virus which withstands boiling is unique The authors deserve credit for this contribution to a difficult problem —Ed]

Guillain Barre Syndrome or Acute Infective Polyneuritis is discussed by C P Petch[5] (St Helier Hosp London) Guillain Barre and Strohl (1916) described a severe form of flaccid paralysis in two soldiers who had complained first of abnormal sensations in the feet then of weakness of the legs

(5) L t 2 405 408 S pt 3 1949

S Light and Horace L Hodes[4] describe in detail studies carried out during six hospital nursery outbreaks in Baltimore and Washington of diarrhea among newborn infants These studies were briefly described in 1943 At that time the authors reported isolation of a filtrable agent in connection with four of these outbreaks which regularly produced diarrhea in calves

In all outbreaks studied the disease appeared to be limited to newborn infants Older infants and adult attendants in the nursery had no apparent diarrhea or other symptoms which could be connected with the newborn infants illness Stomatitis was not a feature in any outbreak studied

Stool suspensions obtained from infants during four of the outbreaks were frozen for several days then thawed and inoculated intranasally into four calves In all four bloody mucoid diarrhea developed Saline suspension of these infected calf stools in roughly 30 per cent dilution was inoculated intranasally into other calves The material was quickly injected into the nose with a syringe the barrel of which blocked the nostril so that there could be no important loss due to sneezing or blowing In 72 of 75 animals used for passa e diarrheal disease developed

Incubation period of the disease in the calf ranged between two and five days There was considerable variability in severity and manifestations of the disease although all calves displayed in common diarrhea with production of mucus usually in large amounts and almost all showed blood at some time during the disease Relapse was an almost universal feature Occurrence of more than one relapse was seen several times Total duration of the disease from onset until stools became and remained normal varied from 8 to 54 days (average 17 21 days)

Eleven calves under age 1 month were exposed to cross infection and in all 11 the disease developed

Attempts were made to inactivate the infective agent with heat A calf which received material that had been boiled directly over a flame for five minutes remained well However on later injection with infectious material this animal

(4) J E per M d 90 113 135 August 1949

duced at times a little difficulty with micturition in the most acute pha e There was never fever when muscle weakness be gan but four patients had had a febrile illness a few weeks earlier Spinal fluid was normal in all respects except for pro tein level which was usually raised sometimes rising as paralysis improved All recovered completely except one pa tient who died following convulsions which developed while respiratory function was still good

Confusion with acute anterior poliomyelitis causes the main difficulty in differential diagnosis but usually the clini cal pictures of the two diseases are distinct The differences are as follows Patients with Guillain Barre syndrome are afebrile and paralyzed when first seen If it is possible to relate onset to an obvious fever such fever has usually developed two or three weeks previously Patients with poliomyelitis are usually febrile at onset of paralysis and for a few days beforehand In Guillain Barre syndrome paralysis at times spreads rap idly but more often slowly whereas the paralysis of polio myelitis is classically maximal at the onset though it may extend especially to the medulla in rare instances In Guil lain Barre syndrome the paralysis is symmetrical or perhaps ascends a little higher on one side Proximal muscles are most affected in the limbs and the trunk usually escapes In polio myelitis a single limb two on the same side or odd groups of muscles are often affected as is the trunk Subjective sensory symptoms are greater and more persistent in the Guillain Barre syndrome than in poliomyelitis but genuine objective sensory loss is not a feature of either disease Recovery though sometimes slow is complete in Guillain Barre syn drome in contrast to the residual paralyses pathognomonic of poliomyelitis There usually is not much muscle wasting in Guillain Barre syndrome and cerebrospinal fluid usually shows an increase in protein without an increase in cells In poliomyelitis there is typically first an increase in cells and later in protein Spinal fluid findings in either disease may be atypical however and therefore make the diagnosis difficult Rarely do other forms of polyneuritis present difficulty in dif ferentiation Diphtheric and alcoholic polyneuritides and lead paraly es can be readily differentiated There is no specific treatment for Guillain Barre syndrome

which made walking difficult These workers drew attention to six features of the syndrome which they regarded as im portant motor impairment abolition of tendon reflexes and preservation of cutaneous ones paresthesias with only slight objective sensory change pain on pressure over muscle masses slight modification of the electric reactions and hyper albuminosis of the cerebrospinal fluid without cellular reac tion For this clinical picture the name polyradiculoneuritis was proposed The description of polyradiculoneuritis by Guillain Barre and Strohl subsequently modified by Guillain in 1936 is identical with that of acute infective polyneuritis given by English workers and the polyneuritis with facial diplegia of which Laurens and American workers wrote

The French however did not admit the identity of the two conditions holding their syndrome to be always benign but this distinction could not be maintained Moreover the supposedly characteristic spinal fluid findings appeared in other illnesses and were not always present in cases that were otherwise typical Guillain for a long time resisted all modi fication of his original specification and stated that he pre ferred to exclude all fatal cases all febrile ones and all those with spinal fluid protein level less than 100 mg /100 ml He accepted the frequency of seventh nerve involvement how ever Later he admitted the possibility of death and agreed that the spinal fluid changes were never in themselves pathog nomonic In America the term acute infective polyneuritis is less commonly used than the eponym Guillain Barre syn drome

Eight patients with this syndrome observed by Petch showed symmetrical flaccid paralysis involving particularly the proximal muscles of the limbs and reaching in severe forms to the cranial nerves with a predilection for the sev enth Subjective sensory changes marked onset of the disease but little objective loss was demonstrated in ordinary tests Tendon jerks were always lost in affected limbs abdominal re flexes being usually preserved and plantar reflexes flexor Ex tensor plantar response claimed by some to be present in early stages and to afford evidence of implication of the upper motor neuron was not seen Sphincters were unaffected but loss of voluntary muscle power and enforced recumbency pro

Studies on Listeria Monocytogenes—*Isolation of Monocytosis Producing Agent (MPA)*—L monocytogenes is the causative organism of a rare disease (more common in certain animals than in man) characterized by a monocytic leukocytosis bacteremia hepatic necrosis and occasional meningoencephalitic involvement Fifteen cases of listeria meningitis in man have been reported Death occurred in nine and recovery in six

Because of the similarity of the hemopoietic response to infection with three different agents (listeria mycobacteria and the etiologic agent of infectious mononucleosis) Neville F Stanley[7] (Sydney) studied the mechanism involved in production of a monocytosis

The MPA of L monocytogenes proved to be part of the lipoid material of that organism This is not surprising as it is known that some lipoids foreign to the experimental animal may act as a stimulus for production of large monocytes American workers have found that phthioic acid a fatty acid fraction prepared from the phosphatides of Mycobacterium tuberculosis specifically stimulates production of mononuclear cells in tissues of man and animals Monocytosis produced during experimental infection of animals with L monocytogenes was of the same order of magnitude as that produced by intravenous injection of the MPA However monocytosis of the infected animal persisted in most experiments for a longer period than that induced by one injection of MPA This was probably due to liberation of lipoid from the growing and dying organisms at the foci of infection in the animal The MPA was serologically inactive and had low tissue toxicity

Role of Listeria in Infectious Mononucleosis—Stanley[8] calls attention to the fact that infectious mononucleosis (glandular fever) may assume several different clinical forms There is still some doubt as to the nature of the etiologic agent The majority of evidence suggests that the disease is caused by a filtrable virus The only noteworthy evidence antagonistic to this theory has arisen from isolation of L monocytogenes from the blood of patients with infectious mononucleosis

(7) A t l n J E p B l & M S 7 1 3 131 Ma ch 1949
(8) Ibid pp 133 142

Epidemiologic Study of Infectious Mononucleosis in a New England College is reported by Alfred S Evans (Yale Univ) and Elizabeth D Robinton[6] (Smith College) Despite an increasingly voluminous number of reports on the clinical and laboratory aspects of infectious mononucleosis articles on actual epidemics are few This suggests either that the contagiousness of infectious mononucleosis as now encountered is low or that the disease may occur in such a mild form as to go unrecognized Recent studies in military camps in this country and in Scotland suggest that for every clinically recognizable case there may be many other subclinical or inapparent infections Therefore the sporadic nature of infectious mononucleosis may be more apparent than real since mild cases may escape detection An opportunity to investigate this possibility recently occurred at Smith College where the number of cases of infectious mononucleosis appeared to be greater during the winter of 1948 49 than in previous years

The incidence of infectious mononucleosis at Smith College has shown a steady increase in the last four years in contrast to the general downward trend of five other common illnesses (virus pneumonia rubeola rubella varicella and mumps) Part of this apparent increase may have been due to increased willingness on the physician s part to make a diagnosis of infectious mononucleosis in the absence of an elevated heterophil antibody titer No general seasonal trend was apparent which is in accord with other reports

A dormitory of 63 residents in which 5 had infectious mononucleosis within a month was surveyed for the presence of subclinical or inapparent infections No evidence that any of the other 58 persons had mild or unrecognized infectious mononucleosis was found The authors therefore conclude that infectious mononucleosis under most circumstances is a sporadic and endemic disease with a low contagiousness It has previously been pointed out that infectious mononucleosis rarely involves roommates Over a 10 year period no such case was noted at several colleges where such studies were carried out

[It is disappointing that so little has been added to our knowledge of this disease despite the efforts of many able investigators —Ed]

(6) New England J Med 242 49 496 M 30 1950

These instances may be too few to be significant yet results of investigation on virus origin of the disease are by no means conclusive Stanley therefore carried out studies to determine whether several strains of L monocytogenes could play any possible role in the etiology of the disease

Twenty consecutive patients with infectious mononucleosis were selected Investigations were designed to determine whether any relation existed between Paul Bunnell titer and presence of agglutinins for listeria whether listeria could be isolated from a patient s blood after diagnosis of infectious mononucleosis had been made by hematologic and clinical means whether presence of listeria agglutinins was due to nonspecific stimulation of antibodies and whether any serologic relation existed between MPA and the patient s serum Blood was collected from patients with a clinical and hematologic diagnosis of infectious mononucleosis It was (1) cultured for organisms (2) tested for agglutinins to sheep red cells by the modified method of Paul and Bunnell (3) tested for listeria agglutinins (4) tested for complement fixing antibodies to listeria MPA and (5) tested for agglutinins to Proteus OX19 Brucella abortus and members of the typhoid paratyphoid group Three strains of listeria were used the Australian strain isolated from a patient who died of meningitis an English strain isolated from a patient with infectious mononucleosis and an American strain isolated from a patient with meningitis

Results showed that Paul Bunnell titers were neither related to severity of disease nor to degree of monocytosis It is usual to find negative Paul Bunnell tests in about 30 per cent of cases clinically and hematologically diagnosed as infectious mononucleosis Positive Paul Bunnell tests were obtained in 13 of the 20 cases in the present series In 7 of the 13 there were significant listeria agglutinations It is possible therefore to classify the 20 cases into three serologic groups those with a positive Paul Bunnell test and listeria agglutination those with a positive Paul Bunnell test and negative listeria agglutination and those with negative responses to both tests The fact that in one case both the Paul Bunnell and the listeria agglutination titer increased over eight days and in another case a decrease in both titers was recorded over

four weeks makes the positive listeria agglutination test in infectious mononucleosis seem more significant

Blood of 17 of the 20 patients was cultured for organisms and L monocytogenes was not isolated from any specimens However the serious drawback in postulating any relation between infectious mononucleosis and L monocytogenes is the inability of the organism to stimulate formation of sheep red cell agglutinins in the rabbit This observation was confirmed and extended to show that the polysaccharide protein and lipoid fractions of L monocytogenes could neither agglutinate sheep red cells themselves nor stimulate production of sheep red cell agglutinins in the rabbit

It is likely therefore that in dealing with so called infectious mononucleosis one is not dealing with one disease but with two or more entities almost indistinguishable clinically and hematologically Stanley concludes that some cases of infectious mononucleosis may be due to infection with L monocytogenes but that the role of listeria in infectious mononucleosis must await further study before a definite answer can be obtained

[Because this bacterium induces a monocytic response in the blood of r bbits several other workers have sought to connect it with infectious mononucleosis So far the evidence is not persuasive.—Ed.]

Etiology of Erythema Nodosum in Children. S A Doxiadis[9] (Univ of Sheffield) presents data on 100 cases to call attention to the importance of recognizing erythema nodo um in children as a valuable sign of tuberculous infection The disease is usually considered a nonspecific manifestation of hypersensitivity to various allergens mainly bacterial Of the infective agents responsible for hypersensitivity in children Mycobacterium tuberculosis is the commonest and streptococcus is second in frequency

Children were tested either by application of tuberculin jelly to the skin or intradermal injection of 0 01 mg or less of old tuberculin If the result was positive no further tests were performed If negative l rger amounts of old tuberculin (0 1 mg) were injected intradermally A positive reaction resulted in 88 children 59 (67 per cent) of whom had other evidence of active tuberculous infection Chest x rays showed

(9) B t. M J 2 844 845 Oct. 15 1949

striking unilateral enlargement of hilar shadows in 54 and in some opacities on the same side as the hilar enlargement consistent with a diagnosis of primary tuberculosis Five chil dren had cervical adenitis in three pus obtained by incision or aspiration contained Myco tuberculosis Within three months after appearance of erythema nodosum pleural effu sion developed in four children there was extension of radio logic signs in the lungs in two miliary tuberculosis developed in one and one child died of tuberculous meningitis Study of the seasonal incidence of erythema nodosum revealed a smaller number of cases in summer and autumn None of the patients had evidence of rheumatic infection and in the 80 observed for at least six months there was no sign of cardiac involvement

Erythema nodosum cannot be attributed with certainty to tuberculosis in the 88 tuberculin positive children However there was a close relation between the eruption and infection at least in the 59 who at the time of eruption had other evi dence of active tuberculous infection This was probably true of the other 29 children These results show that in England most children with erythema nodosum are passing through their primary tuberculous infection

Since special investigations were not made of the 12 tuber culin negative children there is no direct evidence that a streptococcic infection was the main etiologic factor though a sore throat or scarlet fever preceded eruption in 6

Absence of a demonstrable relation between erythema no dosum and rheumatic fever in this series is worthy of empha sis because some physicians still consider erythema nodosum to be rheumatic in origin and fail to investigate further

[There is a marked discrepancy between findings in Britain and America regarding the relation of erythema nodosum to tuberculosis. Here tuberculous infection seems rarely to be the cause.—Ed]

Erythema Nodosum J H Middlemiss[1] observed 124 cases of erythema nodosum from 4 to 48 months Analysis of this series with particular reference to pulmonary changes demon strated radiologically in just under 50 per cent of cases is presented

It is generally agreed that erythema nodosum is not a spe cific disease but is a nonspecific reaction to various infections

(1) B t J Rad ol 22 375 383 J ly 1949

and toxic agents It occurs most commonly in association with primary tuberculous infection It manifests itself as painful nodular lesions on lower or occasionally upper limbs associated with constitutional changes Local lesions are bilateral round or oval swellings usually chiefly affecting shin areas there may be only two or three on each limb or the greater part of the extensor surface of the limb may be covered They are very tender to touch Initially they are deep red but as they fade they become purple and later ecchymotic—the play of colors Constitutional changes include mild pyrexia malaise and sore throat and often joint pains and swelling The acute stage lasts for 7 10 days and skin lesions for 2 3 weeks though they may persist for 4 5 weeks

In the present series erythema nodosum was twice as common among females of all ages as among males In patients over age 15 (older age group) predominance of females over males was 4 1 All patients were given a Mantoux test 1 10 000 tuberculin was first used and in the event of a sero negative reaction successive tests with 1 1 000 and 1 100 tuberculin were made Cases in which x ray appearances were consistent with pulmonary tuberculosis and the Mantoux reaction was positive were regarded as being definitely causally related to tuberculosis These cases numbered 55 Cases in which there was only a positive Mantoux reaction and no other clinical or radiologic manifestation of tuberculosis were regarded in the younger age group as being probably tuberculous and in the older age group as being possibly tuberculous There were 44 such cases Of the 55 cases with demonstrable radiologic changes and positive Mantoux reactions 49 *were associated with primary tuberculous infection* It is believed that in England the possibility of primary tuberculosis must be considered in all cases of erythema nodosum until some other etiologic factor is demonstrated or proved

Attempt to Confirm "in Vitro Cultivation of Rat Leprosy Organism" *Recent experiments indicated that acid fast bacteria can be cultivated from rat leproma after incubation for a few weeks to 1½ years and can be shown to cause rat leprosy following reinoculation into rats* Using similar methods John H Hanks and Mary F Soule (Harvard Univ) were

(2) J J f ct. D e 85 225 2 9 N D 1949

unable to cultivate acid fast bacteria from rat leproma or to produce rat leprosy by inoculating rats with these organisms

[This fail to-confirm note is included because the original report was abstracted last year —Ed]

The Chest

J BURNS AMBERSON M D

PART II

THE CHEST

PROGRESS AGAINST DISEASES OF THE CHEST

A review of the past 10 years during which the YEAR BOOK OF MEDICINE has presented most of the significant reports and studies in this field of clinical medicine testifies to the many sound advances during this time. There have been a few revolutionary changes such as improvements in therapy by the introduction of specific antimicrobial agents but for the most part progress must be credited to the working over of old ground with new and more efficient tools resulting in a perfection and refinement of our knowledge

Physiology —This has been a notable decade in research in human respiratory physiology bringing fundamental knowledge which applies widely in most fields of clinical medicine Precise methods have been developed and tested so that pulmonary ventilation the distribution of gases over alveolar surfaces the diffusion of gases through the alveolocapillary membrane and the mechanics of circulation of blood through the lung can be determined separately The available elaborate methods of study may detect disturbances in these various functions and lead to the identification of the cause of the abnormality Similarly investigations have been extended to elucidate conditions in the major pulmonary blood vessels and the heart. The use of cardiac catheterization has yielded much information concerning the dynamics particularly of the right cardiac chambers including hydrostatic pressures velocity of flow and volume of output. The sequence of events leading to excessive strain of the myocardium and the development of the syndrome known as cor pulmonale has been pursued with success. The clinical picture of pulmonary insufficiency has now become rather familiar After a study of the literature the alert clinician may suspect or detect many of these physiologic disturbances may

have accurate determinations made and then according to his interpretations may plan the treatment of the patient more rationally and usually more effectively than was ever possible before

The increasing use of bronchospirometry although it is still a procedure whose use is confined mostly to specialized hospitals or units adds materially to our understanding of the differential function of the two lungs and is particularly useful when radical surgery is contemplated

One of the chief effects of pulmonary insufficiency is anoxemia *Careful studies have demonstrated the unreliability of* cyanosis as an index Although the direct measurement of blood gases is most precise the oximeter because of its relative simplicity is earning a place in clinical practice where approximate estimates are adequate The importance of intact respiratory function in avoiding the effects of anoxemia which are now so much better understood is emphasized by the demonstration that a red blood cell passing through an alveolar capillary is exposed to the fresh oxygen supply for only an instant i e not longer than 0 1 second

There has been much consideration of the physiologic defenses of the lung against bacteria and other noxious agents Of all those which are assumed or identified the ciliated mucosa of the respiratory passages has been proved to be among the most effective So long as the ciliary mechanism continues operating efficiently the lower respiratory tract is usually well protected Severe damage such as that caused by flames can be expected to be followed by pulmonary complications and even mild damage caused by excessive tobacco smoking has been shown to have its disadvantages

Anatomic studies—Possibly the most important practical development in this field of study has been the more precise identification of the bronchopulmonary segments and their blood supply In clinical diagnosis a familiarity with this anatomy often furnishes a *leading clue For example the finding of un*resolved or chronic pneumonia in a given segment of a lobe *may* be the first evidence of a carcinoma in a subsidiary branch of a lobar bronchus The relative importance of this evidence is great because such lesions are usually beyond the reach of *bronchoscopic* vision and an immediate exploratory operation may be indicated

Certain advances in pulmonary surgery would not have been possible without this anatomic knowledge The preci ion with which a bronchopulmonary segment may be dissected separated from the remainder of the lobe and removed without hazarding serious bleeding or disturbances of ventilation is most impressive

Thoracic surgery—The advances in the realms of respiratory physiology pulmonary anatomy and anesthesia together with the availability of antibiotics has made this decade unprecedented in thoracic surgery The achievements are to be credited also in large part to great improvements in technical skill and training and the teamwork which has been cultivated among all those interested in this field

Resections of lungs lobes segments or blocks may now be undertaken with rather accurate calculation of the risk according to clinical estimation of the patient s general condition phy i ologic limitations existing or likely to result from the operation and the urgency of the condition requiring operation Postoperative alterations of function are better understood more readily identified and more effectively corrected now that experiences have accumulated

Thoracotomy and resection of parts of the lung involve such small hazards that direct lung biopsy is now undertaken when necessary As a rule this is safer than a needle or punch biopsy and has the great merit of enabling the surgeon to select after palpation the best specimen of tissue to take There is of course the possibility that this procedure may be adopted too often as a short cut to diagnosis when adequate and intelligent clinical studies would give the answer

Decortication of the lung which has been locked in a more or less collapsed and functionless condition after hemothorax or some inflammatory process has been practiced more and more to remove the peel which usually consists of fibrinous exudate or a more or less organized fibrous membrane The restoration of pulmonary function by this procedure is sometimes striking This also has the great virtue in some cases of obliterating a pleural dead space which may be an existing or future eat of infection and which previously was managed by extensive and often mutilating p la tic operations on the chest wall

Pneumonia—The revolution in the treatment of pneumonia by the introduction of the sulfonamides penicillin and other antibiotics is a familiar story It is difficult to realize that serum

treatment was the only truly specific therapy in the decade before this one Pneumonia has been robbed of its terror in most cases and the mortality from it has been reduced to a third and less of what it was in previous years The desperately ill pneumonia patient gasping in an oxygen tent is not the familiar scene it once was

New antibiotics keep appearing and although many may have more or less toxicity for some patients the range of selection is such that almost no severe pneumonia need go without the benefit of one or more of them The relative advantages of parenteral or oral administration as compared with aerosols continues to be debated because of the uncertainty of penetration of the latter

The separation of various rickettsial and viral pneumonias has been an achievement of major rank especially since effective specific treatments are now available for a number of them

The outlook for abscess of the lung resulting from necrotizing suppurative pneumonias has likewise changed materially The occurrence of abscess seems to be less although statistics are not available If this is true it is probably due largely to the prophylactic and therapeutic use of antibiotics External drainage of lung abscesses is now practiced much less often than it was 10 years ago This is because antibiotic drugs often help to control the infection then if serious defects of the lung remain in the form of chronic abscesses resection of the lobe or segment is now carried out This has great advantage over older procedures such as plastic operations which sometimes were used in an attempt to repair the defects

Pulmonary mycoses—In the United States the study of coccidioidomycosis and histoplasmosis has occupied the stage during these 10 years The proved frequency of the former infection and the apparent frequency of the latter in certain geographic areas provides an interesting study in epidemiology The fact that the pulmonary lesions caused by these infections which apparently are acquired by inhalation may go on rather rapidly to calcification is an interesting chapter since previously it was assumed that causes aside from tuberculosis were rare The peculiar behavior and relative harmlessness of coccidioidal pulmonary cavities have been well demonstrated and the frequent permanency of recovery from both these infections is one of the features which helps to distinguish them from tuberculosis

Pneumoconioses—The hope that inhalation of metallic aluminum might alleviate the effects of silicosis was proved not to be justified in fact aluminum itself has been shown some times to lead to the formation of foreign body granulomas in the lung

There has been considerable discussion of so called benign pneumoconioses such as those caused by the inhalation of iron coal dust and graphite However while these do not seem to predispose to pulmonary infection as does silicosis they are not entirely benign with respect to the effect on pulmonary function The correctness of the term benign therefore is dubious

The identification of severe pulmonary disease among workers in the abrasive manufacturing industry and among those handling diatomaceous earths particularly after these substances are subjected to very high temperatures has led to the suspicion that the lesions are a peculiar form of pneumoconiosis caused by the inhalation of exceedingly fine particles of free silica and silicates possibly combined with other materials Likewise the investigation of pulmonary disease among beryllium workers has implicated this metal or its derivatives as particularly toxic substances in the lung The facts so far established indicate the need for further studies to explain the peculiar susceptibility of certain individuals The practical problem of course in all these conditions is some adequate means of prevention and it has been heartening to learn that beryllium is to be eliminated by manufacturers from the inside coating of fluorescent lamps apparently a common source of harmful dust or fumes

In this connection mention may be made of apical caps or scars found not infrequently over the dome of each lung Formerly thought to be tuberculous recent investigations indicate that they are often of nonspecific origin and may contain a high percentage of silica However since they are not morphologically like silicosis the significance of this finding remains in doubt

Tuberculosis—This continues to be the most prevalent and disabling infectious disease of man although in various countries such as the United States the mortality has dropped impressively Here and in certain European countries it has been shown that the rate of infection especially among adults has not diminished commensurately with the mortality However

this phenomenon is frequently associated with the postponement of the majority of primary infections to adolescence or adult years Consequently we are seeing more lesions of primary infection in adults Similarly the prevalence of death from tuberculosis has shifted more and more to the older age groups Among elderly men for instance this disease at least in cities has not diminished as a cause of death and in some places has increased

Much fundamental research in tuberculosis has been directed to a better understanding of the conditions under which airborne infection may occur to identification of factors of natural resistance which plays such an important part in protecting the human race and to the best means of prevention of infection and the minimization of its effects once it is acquired BCG vaccination having been found harmless has come into wide use in Europe and parts of other countries It is interesting that the workers in the United States have been more critical of the merits of BCG than have some other national groups and have generally favored its application only among those peculiarly exposed to the infection such as some hospital employes

Studies on the pathogenesis of tuberculosis continue to be fruitful and to justify the prolonged and expensive care of early cases detected before the appearance of symptoms thus usually preventing progression of the disease The percentage of earlier cases diagnosed steadily increases due largely to the availability of photoroentgen units and the organization of case finding by official and voluntary public health groups

The application of the principles of physical chemistry to the study of the tubercle bacillus and its cultivation has yielded a large amount of new knowledge The recovery of the bacillus from various materials has been expedited and considerable information is accumulating regarding the finer differences of virulence and their possible significance The search for some objective test to measure the activity of the infection and the resistance of the patient against it continues Current studies of the serum proteins and of serologic reactions such as hemagglutination have stimulated great interest in this direction

The discovery of streptomycin and other less potent antibacterial agents has marked the beginning of a new epoch in the treatment of tuberculosis Investigations have been extensive and numerous and an impressive amount of knowledge of these

agents has accumulated in a relatively short time The applications and limitations of the drugs and their usefulness with relation to other therapeutic procedures are being learned rapidly

The relative safety with which radical surgery may now be conducted in the thorax has brought within the realm of practicality the resection of tuberculous lungs or parts of them A most significant change is the resection of badly damaged segments or lobes leaving intact ample tissue which is healthy or only slightly affected by the disease These resectional operations promise to save many patients from the chronic destructive effects of tuberculosis but their safe and effective use requires much precise preliminary study of the lesions and great surgical skill The criteria of selection of cases are only now taking form

At the same time the older procedures of pneumothorax pneumoperitoneum and thoracoplasty are being applied with more discrimination than before Pneumothorax for instance is used less often but more wisely The greater availability of various treatments widens immensely the benefits to patients

Neoplasms—Most interest is centered on cancer of the lung which appears to be on the increase and probably is etiologically related to excessive tobacco smoking There is also some hint that chromates arsenic and asbestos when inhaled into the lungs may favor the development of carcinoma although the evidence is not conclusive and there has been no experimental proof There has been a growing sentiment that adenoma of the bronchus is not always benign and should be resected if possible Round lesions which may be carcinomatous and which are discovered mainly in routine x ray surveys of the chest have been the subject of considerable curiosity and debate Some feel that since diagnosis is difficult surgical resection should always be performed This may involve the loss of a lobe or an entire lung unnecessarily since the lesions sometimes turn out to be relatively harmless Other than carcinoma the most frequent consideration is a localized tuberculous caseous lesion which perhaps had best be removed but not with the sacrifice of much healthy tissue this would imply segmental or block resection

A notable advance has been the development of cytologic study of the sputum for exfoliated cancer cells In the hands of expertly trained persons this has afforded early diagnosis in many cases Similarly the perfection of bacteriologic technic

has provided for the more precise and definite diagnosis of tuberculosis in numerous instances

Among the other achievements of these 10 years may be mentioned the prevention and management of pulmonary embolism the physiologic effects of trauma including blast injuries of the chest the mechanism of wet lung as distinguished from atelectasis the identification of the abnormal physiology of hemangiomas and arteriovenous aneurysms of the lung and the indications for resection the better understanding of postoperative pulmonary complications and their correction the preliminary investigation of ACTH and cortisone for their effects on certain pulmonary diseases and the continued investigation of sarcoidosis and search for its etiology

—J Burns Amberson

"Ideal' Alveolar Air and Analysis of Ventilation Perfusion Relationships in Lungs R L Riley and A Cournand[1] (Columbia Univ) state that if the subject is in a steady state the composition of inspired air entering alveoli and of mixed venous blood entering alveolar capillaries is constant throughout all parts of the lungs and can be determined by direct sampling and analysis The composition of alveolar air and of blood leaving alveolar capillaries varies and depends on ventilation perfusion relationships Each different value for alveolar air and alveolar capillary blood is associated with a different value for respiratory quotient (R Q) At the specific R Q which applies to the lung as a whole there is only one value for alveolar and capillary pCO and for alveolar and capillary pO which satisfies both gas R Q and blood R Q equations This value the ideal is the only one which can exist homogeneously throughout all parts of the lungs and be compatible with the quantitative aspects of gas exchange in a given subject

A simple method for determining the ideal point is based on the fact that arterial pCO_2 is essentially the same as ideal alveolar pCO_2 Alveolar pO may be calculated from arterial pCO and R Q a calculation which in effect determines the point on the gas R Q curve at which pCO_2 is that of the arterial blood Thus the calculated alveolar air values are essentially the same as the ideal alveolar air values except under special circumstances A theoretically correct equation derived by *several authors is*

$$\text{alv pO} = \text{insp pO} + \frac{\text{alv pCO} \times \text{insp } 7\text{O} \times (1-\text{R.Q})}{100 \times \text{R Q}} - \frac{\text{alv pCO}}{\text{R Q}}$$

Quantitative estimation of variations in ventilation perfusion ratio depends on the magnitude of the difference between the ideal alveolar air and the mixed alveolar air and mixed capillary blood respectively Were there no such variations the partial pressures of mixed alveolar air and mixed alveolar capillary blood would be identical with each other and the

(1) J Appl d Phy 1 1 825 847 J 1949

ideal alveolar air However ventilation of poorly perfused alveoli causes the composition of mixed alveolar air to diverge from the ideal along the gas R Q line in the direction of inspired air Perfusion of poorly ventilated alveoli causes the composition of the mixed capillary blood to diverge from the ideal along the blood R Q line in the direction of the mixed venous blood It is theoretically possible to quantitate the effects of variations in ventilation perfusion ratio in terms of dead space air admixture and venous admixture

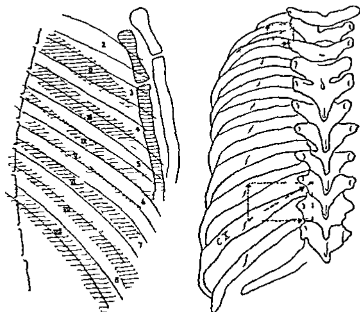
Since mixed alveolar air and mixed capillary blood can not be accurately determined the contributions to dead space and venous admixtures which result from variations in ven tilation perfusion ratio cannot be separated from the contribu tions resulting from anatomic dead space and true venous admixture The combined effects from both contributions must be measured and the usual concepts of dead space and venous admixture expanded Dead space is considered to include not only the anatomic dead space but also the con tribution from alveoli with a high ventilation perfusion ratio Ratio of dead space to tidal air in excess of 30 per cent indi cates that a significant proportion of alveoli are well ventilated but poorly perfused Venous admixture includes not only blood from the bronchial veins thebesian veins shunts etc but also a contribution from alveoli with a low ventilation perfusion ratio The ratio of venous admixture to cardiac output in excess of 7 per cent indicates that a significant pro portion of alveoli are well perfused but poorly ventilated Ventilation perfusion relationships must be analyzed within the normal range of oxygenation since breathing either low or high oxygen mixtures minimizes the effects under consid eration

Studies on Respiratory Mechanics Francis Polgar[2] (Yale Univ) states that biaxial rib movements consisting of abduc tion around a vertical and elevation around a horizontal axis is the basic phenomenon in rib movements in man During the whole course of phylogenetic development this mechanism is utilized to facilitate respiratory movements of the thorax The role of the diaphragm is secondary

The different bony structure of the upper and lower hemi thorax accounts for different manifestations of the two basic

(2) Am J Roentgen 1 61 637 657 M y 1949

movements in the respective parts of the chest Horizontal in crease of chest volume results from widening a result of abduction of the ribs and deepening due to forward propul sion of the breast bone and dorsal displacement or repulsion of the manubria Propulsion is a secondary movement caused by elevation of the ribs but repulsion is the direct effect of



F g 13 (l ft) —D g am t w g p at y d pe g f b cag a h lthy ma D p g m h m p u d s p r or h m th a th ngl f Lou dec se i p t
F g 14 (ght) —D g mm t pla t u f gm nt l h g f h ma I a to sy t m Th b l t nd el u se f th ho tal bd ct g for mpo nt f th l tor the l w h mith x.
(C t y f P lg F Am J Roe tge l 61 637 657 M y 1949)

extramural muscular forces Abduction is checked in the supe rior hemithorax because of the mechanics of the upper limbs which require strongly attached two headed ribs Elevation (Fig 13) is favored there and promoted by the suitable ar rangement of bony and muscular components Formation of the inferior hemithorax mainly promotes abduction while making possible horizontal enlargement by means of repulsion of the costal manubria

The function of the costotransverse joints is of great im portance in this mechanism They are saddle joints which allow the ribs to follow a principal course The buffer like construction of the transverse processes in the superior and the shortening and decline of the ribs in the inferior hemi thorax checks and directs their activity By placing the hand on a table with the ulnar border down as if clasping a tumbler and spreading the curved fingers as if enclosing a larger diam eter the stretched fingers move away from one another in a fanlike manner imitating the inspiratory movements of dorso-axillary rib portions

The neck axis theory of rib movements which has been disproved by the preceding observations assumes that the intercostal muscles move the ribs The biaxial theory demon strates that the levatores costarum muscle system is the most effective and essential motive force of inspiration In man these muscles are arranged so that their thickness and length increase gradually from above downward Resolving the pulling force of the oblique muscle by the parallelogram of forces (Fig 14) the vertical elevating and the horizontal ab ducting components can be distinguished

Pathophysiology of Respiration after Lobectomy and Pneumectomy P H Rossier and A Buhlmann[3] (Univ of Zurich) investigated pulmonary function before and after operation in 20 cases of lobectomy and 15 of pneumectomy for bronchiectasis lung cyst tuberculous cavity tumor and atelectasis Under basal metabolic conditions a closed spirom eter system (Mean s double spirometer) was used and the respiratory frequency minute volume oxygen consumption carbon dioxide elimination vital capacity and maximal respir atory capacity were determined To accustom the patient to the apparatus examination was done on two different days At the second sitting about 20 cc arterial blood was taken anaerobically and its oxygen and carbon dioxide content and pH were measured From spirometric and blood values alveo lar function particularly alveolar ventilation and functional dead space was determined

Lobectomy cases comprised 9 women and 11 men and ex amination was performed at least three to four weeks after operation when patients were no longer bedridden Respira

(3) Schw Zt h f T b k 7 1 16 1950

tory reserve is not reduced as much in men as in women Absolute figures for the decrease in vital capacity are about *the same for both sexes* 1 000 1 200 cc Because of the higher initial values the maximal respiratory capacity of men under goes *a greater absolute decrease and amounts to an average of* 50 L as against 20 L in women It is concluded that the *respiratory reserve contraindicates lobectomy only when it is* already considerably decreased before operation Arterial *blood of 12* patients before and *after* operation was normal and except for the decrease in respiratory reserve their pul monary function underwent no actual changes on the other hand lobectomy may result in aggravation in certain cases as observed in 3 patients who had partial insufficiency *Par* ticularly interesting are four cases in which a vascular short circuit or a partial insufficiency caused an arterial oxygen deficit which disappeared after removal of the diseased lobe Thus a vascular short circuit or pronounced irregularity of ventilation may be considered an additional indication for lobectomy

The 15 pneumectomies were mostly in women with bron chial tuberculosis and men with bronchial carcinoma and partial or total atelectasis of the involved lung In six patients thoracoplasty was performed on the side of the removed lung to avoid shifting of the mediastinum and exaggerated infla tion of the remaining lung Pulmonary disease had already caused a 40 or 60 per cent decrease *in* vital capacity and max imal respiratory capacity after operation the vital capacity was further *decreased by only one* fourth an *average of* 460 cc and the maximal respiratory capacity showed no signifi cant change Decrease *in vital capacity is less* the result of a decrease in the total capacity than of an increase in the residual *air Pulmonary inflation following pneumectomy pro* duces an increase in functional dead space The relation be *tween* pulmonary inflation and *dead space is even more* apparent when the former is reduced by thoracoplasty the *functional dead space then amounts* to *only* one *half the value* before pneumectomy From the functional viewpoint thora coplasty after pneumectomy is consequently an advantage since reduction of the dead space ventilation means an economy *in breathing Minute volume is* also decidedly *smaller after* thoracoplasty than after pneumectomy alone The regular fall

in carbon dioxide tension after pneumectomy and thoracoplasty is striking and is causally connected with the decrease in functional dead space If there is a vascular short circuit before pneumectomy it is expected to disappear with the removed lung this results in functional improvement and in this case too the carbon dioxide tension is greatly decreased after thoracoplasty

***Effect of Intermittent Positive Pressure Breathing on* Respiratory Gas Exchange** was studied by Hurley L Motley Leonard P Lang and Burgess Gordon[3a] (Jefferson Med College) by means of arterial blood determinations and expired air analysis on 77 patients with varying degrees of emphysema and fibrosis Determinations were made during both ambient and intermittent positive pressure breathing using compressed air All patients showed a significant rise in arterial oxygen saturation with intermittent positive pressure breathing and correspondingly the oxygen partial pressure (pO_2) of the arterial blood was increased The latter was more pronounced in patients without emphysema

In 14 patients without emphysema and with a transfer gradient over 20 mm Hg the alveolar pO increased from 101 to 111 mm Hg and the aeration gradient dropped 5 mm Hg during intermittent positive pressure breathing The transfer gradient decreased 7 mm Hg and the arterial pO increased 17 mm Hg These findings indicate that a more uniform alveolar ventilation was provided by intermittent positive pressure breathing a factor which explains the rise in arterial pO_2 and the decrease in the transfer gradient since emphysema was not a problem Fourteen patients without emphysema and with a transfer gradient below 20 mm Hg showed similar findings In 28 patients with significant emphysema and a transfer gradient greater than 20 mm Hg the average residual air was 47 9 per cent of total lung volume In this group intermittent positive pressure breathing produced no change in the aeration gradient the alveolar pO increased 5 mm Hg by pressure breathing and the abnormally high transfer gradient of 29 mm Hg decreased 2 mm Hg In 21 emphysematous patients with an average residual air of 48 7 per cent of total lung volume and a transfer gradient less than 20 mm Hg intermittent positive pressure breathing produced a pro

(3a) A t M d 24 14 27 Feb ary 1950

nounced increase in the alveolar pO_2 (86 103 mm Hg) the aeration gradient decreased 12 mm Hg and the transfer gradient increased from 13 to 23 mm Hg

This evidence suggests that intermittent positive pressure breathing increases the arterial oxygen saturation and decreases the mean oxygen gradient of pressure from alveoli to arterial blood by producing a more uniform alveolar aeration inflating those alveoli with impaired circulation of air and mechanical obstruction by fibrosis Apparently the distribution factor is responsible for the elevated alveolar arterial gradient in anthracosilicosis rather than a true diffusion difficulty with increased resistance of the pulmonary membrane

[This is a convincing demonstration of the nature of the re piratory difficulty in the e patients A factor which appears to explain in part the uneven distribution of inspired air is the presence of chronic bronchitis a common complication The accumulation of vi cid secretions and exudate in the bronchi interferes with uniform ventilation of the alveoli —Ed.]

Intrapulmonary Mixing of Helium in Health and in Emphysema. D V Bates and Ronald V Christie[3b] (St Bartholomew s Hosp London) consider that the rate of inert gas mixing is influenced by the effect of the trachea and larger bronchi (anatomic dead space) which prevents a proportion of inspired air from coming in contact with alveolar air and by unequal ventilation of the lungs Experiments indicate that in normal persons the influence of the first factor is sufficient to result in an average mixing efficiency of 76 per cent

In emphysema the impairment in mixing efficiency is much greater than can be accounted for by the comparatively slight increase in anatomic dead space which occurs in the disease Experiments with a model lung show that an increase in dead space of 170 cc lowers mixing efficiency by only 19 per cent whereas there is a difference of 50 per cent between the normal and emphysema groups An increase in anatomic dead space is probably not a significant factor in impairment of mixing in emphysema but one cannot state with certainty that it plays no role

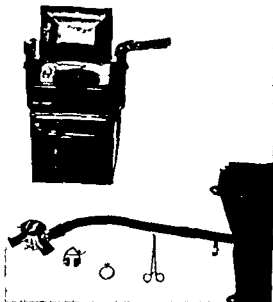
Unequal ventilation in the lungs is mainly responsible for impairment in mixing efficiency in patients with emphysema In 20 patients with emphysema and exertional dyspnea the average mixing efficiency was 25 per cent It is not possible to

(3b) Cl n. S 9 17 29 F b 28 1950

state precisely what proportion of the lung is underventilated in any given case

[While loss of elasticity and other structural alterations may cause unequal ventilation the factor of chronic bronchitis also may play a part (p 170) If so treatment of the bronchitis may materially improve ventilation and relieve symptoms —Ed]

Simple Tests of Ventilatory Function for Use in Sanatorium or Clinic are described by Frederick C Warring Jr[4]



F g 15—App t 100 L Dougl bag h gh v loc ty o way l e con ect g hose and pl ng l p e t d g m t a d st p w t h (Cou t sy f Wa g F C J Am R v T b 60 149 167 A gust 1949)

(Laurel Heights State Tuberculosis Sanitorium Shelton Conn)

METHOD —The apparatus required is illustrated in Figure 15 and can be purchased for about $200 The patient s ventilatory function is evaluated by determining walking ventilation maximal breathing capacity the ratio of these and its relation to dyspnea and careful fluoroscopy of the chest

Walking ventilation is ascertained by having the patient walk at a slow pace *180 ft /minute on a level surface breathing as easily* and naturally as possible through the one way valve into the Doug

(4) Am. R T be c 60 149 167 A g t 1949

las bag After applying the nose clip the patient walks for one minute beside the operator who carries both bag and valve Then the patient and operator continue to walk at the same pace the patient placing the mouthpiece of the valve in his mouth and the operator resetting his stop watch As he walks for the next three minutes the patient breathes in a natural manner through the valve into the bag which is carried by the operator At exactly the end of this period the valve is taken from the patient s mouth the connecting hose to the bag clamped off and the nose clip removed The patient is immediately questioned about the presence and degree of dyspnea which is graded as none slight (aware of labored breathing but not uncomfortable) moderate or severe (could not continue walking or did not complete the test) The air in the Douglas bag is measured by running it through a gas meter calibrated in liters The resulting figure divided by three is the walking ventilation in liters/minute Most patients have a walking ventilation in the range of 12 19 L /minute It is important that in most of them walking ventilation remains remarkably constant A patient can be expected to have closely similar values before and after spread or clearing of disease or collapse therapy

Maximal breathing capacity is determined by having the patient breathe as hard and fast as he can for exactly 30 seconds through the high velocity one way valve into the Douglas bag Air in the bag is measured by passing it through the gas meter the resulting value multiplied by two gives the maximal breathing capacity in liters/minute For healthy males this value is about 150 L /minute and for healthy females about 100 L /minute Any disease or condition which impairs the function of pulmonary or thoracic apparatus proportionately reduces maximal breathing capacity The test should be repeated on the same day or later if both operator and patient are not satisfied that the exertion has been maximal

Dyspnea on walking becomes severe as the ratio of walking ventilation over maximal breathing capacity exceeds 0 50 Therapy that reduces a patient s maximal breathing capacity to a level lower than twice his walking ventilation results in severe dyspnea when he is walking

After these tests the patient is carefully examined by fluoroscope and the chest viewed during quiet breathing slow and rapid maximal inspiration and expiration Movements of the ribs and diaphragm shift of the heart and mediastinum and evidence of trapping of air in a lobe or lung are noted In a patient with pneumothorax the degree of collapse motion of the collapsed lung and presence of fluid are noted Rib and diaphragm motions of each hemithorax are recorded separately in percentages of normal as estimated by the operator By adding the percentages of motion on each side the

ratio of the ventilation carried on by each lung separately can be estimated

These ventilatory studies including careful fluoroscopy are sufficiently accurate for evaluation of pulmonary function in all but the exceptional case It was correctly predicted in all but 2 of 123 patients that thoracoplasty or pulmonary resection would not result in severe dyspnea during post operative walking To avoid dyspnea after thoracoplasty the patient should be left with a maximal breathing capacity of not less than 30 L/minute no matter how low his walking ventilation may be When the maximal preoperative breathing capacity is high the reserve is ample and no concern need be felt about thoracoplasty When it is only moderately high or even lower it is feasible to perform thoracoplasty if the operation is to be done on a poorly functioning side Thoracoplasty can be performed while pneumothorax is maintained on the contralateral side if serial tests of ventilatory function are used to maintain the degree of pneumothorax at a satisfactory functional level to decide if thoracoplasty can be performed and to evaluate the end results of function after operation and subsequent expansion of the pneumothorax lung Ventilatory tests can demonstrate the inadvisability of thoracoplasty for some patients As a guide to additional treatment the maximal breathing capacity can be determined 7 13 days after individual thoracoplasty stages

Ventilatory studies are used in much the same manner in selecting patients for resection Many patients do not require a space filling thoracoplasty after pneumonectomy if protecting the function of the remaining lung is the sole objective These studies are of use in pneumothorax patients to determine the ability of the patient to tolerate this type of treatment to regulate the degree of collapse and to evaluate the patient s eventual breathing capacity when the lung is expanded They are also useful for determining whether phrenic paralysis or pneumoperitoneum should be instituted Temporary phrenic paralysis usually can be expected to lower the maximal breathing capacity 10 15 L and pneumoperitoneum reduces it not more than 5 L

[The simplicity and ease of this method of study of pulmonary ventilation commends it for practical application The ventilatory test alone does not give information concerning distribution of gases in the lung or the alveolocapillary gas exchange Such an estimation requires more compli-

cated tests but if ventilation is measured other disturbances can be more readily suspected on clinical grounds —Ed.]

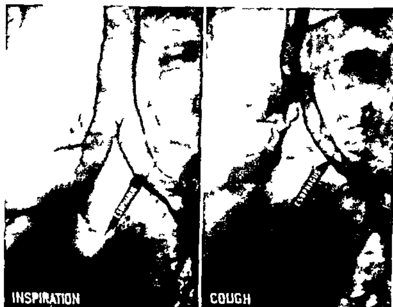
Bronchial Dynamism. S Di Rienzo[5] (Cordoba Argentina) has introduced a contrast medium into the bronchial tree of patients and by obtaining multiple serial and spot films during various respiratory processes has studied the dynamic functions of the bronchi Fluoroscopically it may be observed that while injecting the iodized oil into the air tubes the opaque medium flows into the trachea and major bronchi by the action of gravity but when the medium reaches the secondary or lobar bronchi the flow is pulsating and rhythmic with the respiration When the medium reaches the branches of still smaller caliber there is a forward and backward movement the oil advancing during inspiration and partially receding during expiration Under normal conditions inspiratory advance is greater than expiratory recession but with disease these movements may be absent or equal This inspiratory progress of the opaque medium is due solely to thoracic alveolar aspiration The bronchographic images are normally changeable transitory and nonpermanent and if the usual succession does not occur in any one branch it is because some pathologic factor has intervened and the dynamism of the branch has decreased or disappeared The normal bronchographic picture of the alveoli is one of fine dots and after a certain brief time this fine granulation becomes confluent and thickened The dots should appear simultaneously in every part which is reached by the opaque medium at the same time and must not be irregular The canalicular images are only transitory but the alveolar images are permanent

Normally the bronchial caliber changes during the respiratory movement increasing during inspiration and decreasing during expiration These modifications occur in the large as well as in the finer bronchi The process is uniform all along the bronchial wall but at the end of expiration reduction of caliber is accentuated at the root of the branches especially those of the second or third order and in the alveolar ducts This contraction is due to the presence of muscular sphincters and is common in patients with chronic bronchitis asthma or allergy and in those who have inhaled toxic gases Changes in bronchial caliber are associated with breathing

(5) Rad 1 gy 53 168 186 A gu t 1949

coughing and crying and may be segmental or annular They regulate the entrance and exit of air or secretions into the bronchial branches

From these studies it has been conceived that a cough is a dynamic act of the mucous membrane which expels air or secretions by means of a high speed peristaltic wave originating in the small bronchi and ending in the larynx accompa



F g 16 (l ft) —B o h g am taken d g p t on
F g 17 (ght) —B n h g m t ken d g ough
(Co t y f D R n S P d ol gy 53 168 186 Aug t 1949)

nied by harmonic movement of the functional sphincters (Figs 16 and 17) It is not the increased tension in the bronchi that expels the air and secretions during coughing for expulsion is accomplished by the peristaltic wave in the bronchus Modifications of bronchial caliber during coughing may be very irregular some segments showing no reduction in their anterior diameter while adjacent segments may show strangulation Cough may take place separately in each lung or even in each lobule indicating that there are nerve centers independent of those that govern diaphragmatic contraction

and the muscles of the thorax The esophagus is apparently not influenced by the act of coughing

Bronchial branches which have been destroyed by infection or modified by bronchiectasis do not expel their contents during cough for they have lost their dynamic properties Nothing can be evacuated from ectatic portions in which smooth muscle mucous elastic and nerve tissue have been destroyed by the disease Thus study of the dynamic characteristics of bronchi makes possible differentiation of reversible bronchiectasis susceptible to medical treatment from the irreversible disease which must be submitted to surgery

[*This is an extremely interesting and informative article on the dynamics of the bronchi An understanding of this subject is important in consideration of many pulmonary diseases and their treatment*—Ed]

DIAGNOSTIC AND THERAPEUTIC PROCEDURES

Respiratory Impairment and Pulmonary Complications in Paralyzed States Method for Early Detection Observations by Roy Laver Swank[6] (Harvard Univ) on five patients with severe respiratory impairment the result of paralysis indicate that early impairment is difficult to diagnose by physical examination Although clinical evidence of respiratory failure appears to develop acutely respiratory measurements reveal striking indications of impaired function many hours or even a day before When respiratory impairment is recognized clinically pulmonary atelectasis is probably present

The five patients showed progressive changes in graphic records of the respirations made with the Benedict Roth apparatus Vital capacity and tidal air became reduced to about 1 000 and 350 cc respectively Rhythmic variations in the depth of the tidal air and periodic deep breaths of 500 700 cc appeared in the respiratory records Periodic deep breaths then disappeared and atelectasis followed The rhythmic alterations in the depth of breathing disappeared and the tidal air became uniform in amount at between 220 and 250 cc It could be increased little if at all by maximal effort There

(6) *Am J M Med* 32 229 2 February 1950

were labored breathing cyanosis and rapid failure of respirations

If conditions which lead to pulmonary complications are recognized early and severely impaired respiratory function does not develop or has existed only a few hours use of the respirator can be lifesaving The latest stage at which such therapy can be employed is when periodic deep breathing disappears If pulmonary complications have been present for a day or longer atelectasis with superimposed pneumonitis will probably spread despite use of the respirator Presence or absence of infection may determine whether an area of atelectasis can be re expanded in the respirator

[Promotion of drainage and prevention of stagnation of fluids in the air passages are so necessary in conditions of this type One can easily visualize the impairment of drainage which is likely to occur in paralyzed states See Di Rienzo this YEAR BOOK p 175 —Ed]

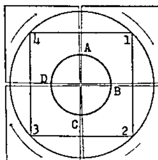
Rotating Kymograph for Study of Pulmonary Cavities Lopo de Carvalho Ayres de Sousa and Carlos Vidal[7] (Lisbon) constructed a kymograph using a screen with crossed slits (Fig 18) behind which the film moves in a clockwise direction describing an arc of 90 degrees and registering by concentric curves the influence exercised on the cavity by any movement produced at a certain distance

TECHNIC —The intersection of the crossed slits is made to fall on the center of the cavity by the following maneuver A thin wooden board on which two wires are fixed perpendicularly to each other with a small lead disk at their junction is inserted in the frame provided for the screen and with the aid of the fluoroscope the lead disk is placed over the center of the cavity A roentgenogram taken at this time shows the points reached by the kymographic slits greatly facilitating interpretation of the kymogram The board is replaced by the screen and the kymogram is taken while the patient breathes slowly

The kymographic registration fixes on quadrant 1 upper costal movements and displacements of point *A* on quadrant 2 mediastinal oscillations and displacements of point *B* on quadrant 3 elevation of the diaphragm and displacements of point *C* and on quadrant 4 lateral movements of the thorax and displacements of point *D*

The kymogram of a large cavity of the right lobe (Fig (19) shows ample movements in the upper and two lateral quadrants and immobility in the lower quadrant During breathing movements of the costal wall and mediastinum act on the cavity walls but the diaphragmatic contractions do

(7) Schwe Zt h f T b k 6 988 1949





F g 18 (l ft) —S h m f a kymog ph w th d I t
F g 19 (ght) —R tat g kymog m f pulm y e n Osc ll t w de uppe d tw l t l q d t
(C te y f d C lb L t l S hw Zt h f T be k 6 9 88 1949)

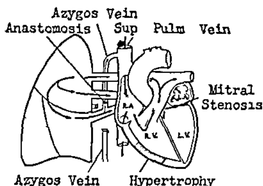
not influence the site of the lesion The mechanical trauma can only be eliminated by thoracoplasty involving all the upper costal arches associated with extrapleural apicolysis according to Semb A small contralateral pneumothorax may be necessary if the cavity does not disappear completely

[This is a clever device for study of the movement of the walls of pulmonary cavities A good deal can be learned al o by s mple fluoroscopy Such observations may yield information about the kind and probable usefulness of collapse therapy even if the observer does not have much faith in the effects of contralateral pneumothorax —Ed]

Surgical Relief of Congestion in Pulmonary Circulation in Cases of Severe Mitral Stenosis Preliminary Report of Six Cases Treated by Means of Anastomosis between Pulmonary and Systemic Venous Systems Richard H Sweet and Edward F Bland[8] (Massachusetts Gen l Hosp) point out that about 10 per cent of persons with rheumatic disease of the mitral valve ultimately develop marked stenosis and although some may not experience striking symptoms others have attacks of pulmonary edema precipitated by menstruation pregnancy intercurrent infections fever or tachycardia induced by emotional disturbances or unaccustomed physical exertion The phenomenon depends on the concurrence of

(8) A S g 130 384 397 S ptembe 1949

long standing mitral stenosis with right ventricle hypertrophy and continuous increase in pressure within the pulmonary circulation Under conditions of stress the strong right ventricle forces the blood into the lung so as to increase greatly the already elevated pressure within the pulmonary vessels and inevitably there is transudation of fluid and often of blood into the pulmonary alveoli producing the clinical picture of pulmonary edema When the attacks occur frequently the patient lives in jeopardy and is forced to adopt a program



F g 20 —P lmo ry a ygo enou sh t S hem t c d gr m to show mecha l eff ct of sh t b tw n p lmo y a d sy tem c culat ns p od c d by nastomo betw n yg e n nd ight nf or p lm n v A ow h ws th t some f blood n fe p lmo y vein i forc d by h gh p s e p lm y c cu t to nter ygo e n through sh t th s l g t some t t p l m nary p e s (C rt y of Sweet R H nd Bl d E F Ann. Su g 130 384 397 S pt mbe 1949)

of limited activity even though the heart muscle remains competent Such patients often die of pulmonary failure rather than failure of the heart itself For such patients a release of pressure in the left auricle such as might result from an astomosis between the cardiac end of the pulmonary vein and the cardiac end of the severed azygos vein might produce a desirable effect on the lung congestion (Fig 20)

Of the six patients on whom this operation was performed two were treated too recently for a satisfactory evaluation of results and one died of an exacerbation of rheumatic fever The other three were greatly improved and none has had an attack of pulmonary edema since leaving the hospital all had been semi invalids preoperatively and two were unable to carry on outside the hospital All are now leading normal

lives Exertional dyspnea and palpitation have diminished It has been demonstrated on the operating table that the shunt significantly lowers pressure in the left auricle but how great a reduction in intra auricular pressure can be induced without impairment of the peripheral circulation is not yet known although present experience has not suggested that any unfavorable result has been produced In one patient catheter studies demonstrated a continuation of the decrease in pressure in the pulmonary circuit after establishment of the anastomosis

[One of several operations now under study for the relief of the functional effects of mitral stenosis this particular operation leaves the primary defect in the mitral valve unchanged There have been some dramatically favorable results of operations on the valve itself —Ed.]

Continuous Postural Drainage Essential Principle in Treatment of Diseases of Respiratory Tract. Among 360 patients with persistent bronchitis basal bronchitis unresolved pneumonia pulmonary fibrosis chronic pneumonitis or bronchiectasis L Bedford Elwell[9] (Brisbane) noted that 96 6 per cent gave a clear history of at least one and often repeated previous attacks of inflammatory chest disease most frequently bronchitis and a considerable portion had the earliest attack in childhood When continuous postural drainage was used by 416 such patients complete symptomatic relief was achieved by 19 7 per cent 59 6 per cent were much improved and 17 6 per cent improved

METHOD —A minimal 18 in. elevation of the foot of the bed is desirable in all chest conditions in which the lower lobes are mainly involved In asthma elevation to 24 in may be necessary before full relief is obtained For drainage of the maxillary antrums 15 16 in may suffice It is always better to manage without a pillow under the head since it tends to slip under the shoulders and interfere with adequate slope of the thorax If there is any tendency for the patient to slide downward a firm bolster or pillow may be required between the top of the head and the end of the bed Most important is to avoid a sagging mattress Tight wire springs and a firm mattress of fiber or tight kapok are recommended If there is any tendency for the mattress to slip it must be fastened to the foot of the bed A firm and watchful parent can usually train young children to lie lengthwise rather than crosswise in the bed but use of tapes and sand hoes is valuable for refractory subjects

The chief aim is to obtain the freest possible drainage of all accumulated and accumulating secretions from the affected area whether lung or perinasal sinus The main outlet must be dependent If the affected areas are multiple most of the time may be spent

(9) M J A t ha 1 804 809 J 18 1949

prone or semiprone as the posterior base bronchi are usually especially involved part of the time may be spent in supine or partly supine and partly lateral position when ventral bronchi lingula bronchus or middle lobe bronchi are affected If the patient states that he avoids a given position because it always provokes severe cough pain or difficult breathing he must be encouraged to spend an increasingly long period in this position taking sedatives if necessary so that he can expectorate quantities of phlegm that he had never been able to discharge before and thus relieve both cough and difficult breathing Drainage of cavities in pulmonary tuberculosis is especially facilitated by this method If the posture is invariably maintained during hemorrhage the hemorrhage clears up much more promptly than without postural treatment Although postural drainage should obviously follow most operations on sinuses or chest if it is consistently applied in the beginning much radical surgery may be avoided

[The merit of postural drainage is great in conditions such as bronchiectasis in which the cleansing mechanisms are severely damaged. In chronic cases it is desirable to have the patient continue postural drainage at least at intervals even though there is little or no yield of sputum This will prevent stagnation of fluid and exudate in the damaged bronchi which provides a favorable medium for renewed infection —Ed]

Aerosol Therapy in Treatment of Postoperative Pulmonary Atelectasis is recommended by H E Christie J F Meakins and M Aronovitch[1] (Montreal) They believe that postoperative pulmonary atelectasis can often be relieved more comfortably for the patient and more easily by medical means than by bronchoscopic aspiration Medical treatment is founded on the premise that the atelectasis is due to tenacious mucus plugging of the bronchus and that generalized bronchospasm tends to hold this plug in place Treatment attempts to do four things (1) liquefy the mucus plug (2) release the bronchospasm (3) allow the liquefied plug to slip out by gravity and (4) reinforce these measures by the expulsive force of cough These steps are accomplished by instituting the following (1) an expectorant mixture (2) a bronchodilator (e g epinephrine) (3) posturing the patient to allow gravity to take effect (4) encouraging cough Sulfonamides and antibiotics are used as indicated throughout treatment

Twenty three patients with postoperative pulmonary atelectasis were given aerosol therapy for bronchodilation Aerosol was administered in 1 cc amounts every two or three hours five to eight times a day A suitable nebulizer of the

(1) Canad M A J 61 388 394 October 1949

DeVilbiss no 40 or Vaponephrine type was used The pressure source for the nebulizer was an oxygen cylinder Insertion of a Y tube at a convenient place in the rubber tubing enabled the patient to produce the aerosol at will The solution used was epinephrine 1 per cent and ephedrine 1 per cent in proportion of 1 9 in nine cases neo synephrine* 1 per cent in 11 cases and various combinations of these drugs in the other three cases Penicillin 20 000 50 000 units streptomycin 50 000 200 000 units or both were not infrequently dissolved in the aerosol solution The treatment was supplemented with bronchoscopic aspiration in five patients

Results were excellent in 17 of 23 patients with complete clinical and radiologic recovery in one to seven days In 10 of these patients re expansion of the affected lobe occurred in less than four days Results were fair in four patients with recovery in 11 17 days clinically and 11 21 days radiologically Two patients had poor results with re expansion in 12 weeks both had bilateral bronchiectasis

[Diminished respiratory movements during and after operation may favor the accumulation of fluid in the air passages which seems to be the chief factor favoring infection The procedures suggested by these authors are reasonable and are usually efficacious —Ed]

Relative Effectiveness of Parenteral, Intratracheal and Aerosol Penicillin in Chronic Suppurative Disease of Lung Edward A Gaensler John F Beakey and Maurice S Segal[2] (Tufts College) report results in four cases of bronchiectasis and lung abscess in which 100 000 units penicillin was given by different routes and urine blood and sputum were assayed for penicillin content In none could penicillin be detected in the sputum after intramuscular injection but after aerosol or intratracheal administration significant penicillin activity was noted in the sputum (Fig 21) for long periods Such findings are consistent with the clinical impression that parenteral therapy is not effective treatment for chronic purulent disorders of the lung X ray and clinical improvement following intravascular therapy in lung abscess and bronchiectasis is probably due to resolution of the surrounding pneumonitis rather than to a real penetration of abscess cavities

Since parenteral penicillin does not penetrate the rigid thick avascular wall of the chronic lung cavity penicillin should not reach the general circulation from within the cav

(2) J Th S g 18 546 560 A g 1949

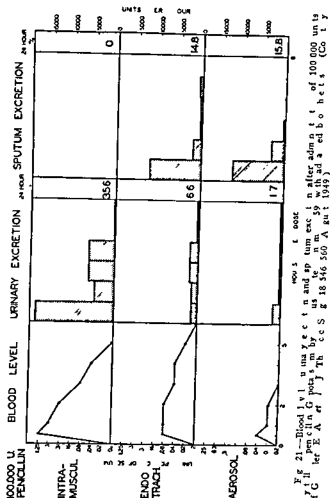


Fig 21—Blood l v l u ina y e c t n and sp tum exc t n after adm n t t of 100 000 un ts pen c ll n G pota s m by us te n m 59 w th ad a ed b o h e t s (Co t y ler E A et J Th c c S g 18 546 560 A gu t 1949)

ity Since the average total urinary excretions in these patients compare favorably with those following similar administration to normal volunteers absorption of penicillin must be from uninvolved portions of the lung A sizable portion of the penicillin was lost in the sputum because expectoration was encouraged This explains why blood level and total urinary excretion values are somewhat lower with aerosol and intratracheal administration

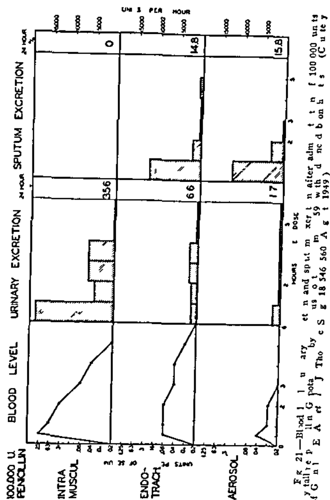
Since the parenteral route is ineffective as a means of treating chronic lung suppuration direct medication must be utilized to alter favorably the pathologic conditions The endotracheal method has several disadvantages which include the liability of sensitivity to topical anesthesia suppression of cough reflex by anesthesia and irritation and edema of the vocal cords which may follow repeated manipulation with a catheter However intratracheal therapy is indicated when endotracheal intubation is necessary for other reasons such as bronchoscopy or bronchography during routine postoperative tracheal aspiration or where rapid improvement of symptoms and reduction of sputum are necessary such as before resection for bronchiectasis or abscess

The chief disadvantage of the aerosol method is its considerable wastage of penicillin Adequate therapeutic concentrations of penicillin may be delivered to the site of the disease by both the intratracheal and aerosol methods Good levels are maintained for about five hours with intratracheal injection and three hours after aerosol administration Since it is questionable whether too high concentrations of penicillin are necessary or even desirable in the re piratory tract repetition of aerosol therapy rather than intratracheal injection appears to be the more practical method More than adequate concentrations of penicillin can be maintained in purulent lung cavities with inhalation of 100 000 units and possibly smaller doses every three or four hours Another advantage of this method is that most patients quickly learn how to use the aerosol apparatus and can if necessary continue this form of treatment at home

[The complex ty of this problem is s lf-evident If inflamed and necrotic areas of the lung are not ell ventilated as is often the case it is unl kely that inhaled aerosol v ll penetrate there very deeply as compared with healthy areas It may be necessary n the individual ca e to u e different routes of administration alternately in order to ascertain wh ch seems to be *best* —Ed]

Biopsy of Diffuse Pulmonary Lesions Diffuse extensive bilateral pulmonary lesions producing minimal symptoms and frequently found on routine roentgen examination present a challenging diagnostic problem In 50 patients Karl P Klassen Alexander J Anlyan and George M Curtis[3] (Ohio State Univ) were able to diagnose such lesions with certainty

(3) A h. Su g 59 694 04 S pt be 1949



ity Since the average total urinary excretions in these patients compare favorably with those following similar administration to normal volunteers absorption of penicillin must be from uninvolved portions of the lung A sizable portion of the penicillin was lost in the sputum because expectoration was encouraged This explains why blood level and total urinary excretion values are somewhat lower with aerosol and intratracheal administration

is placed at the apex of the biopsy site 2 cm. from the lung margin Two Carmalt hemostats are now applied with the tips approximating the placed mattress suture isolating a wedge of pulmonary tissue which is sectioned and removed (Fig 22 3)

The two ends of the suture are now run down as an over and over stitch to the periphery of the lung on each side (Fig 22 4) The Carmalt clamps are removed the suture pulled tight and the two ends tied to bring the cut surfaces together (Fig 22 5) One end of the suture is used as a continuous Cushing stitch to appose the visceral pleural surfaces first on the superior surface (Fig 22 6) and after transfixion at the site of the first mattress suture back to the edge of the lobe on the inferior surface (Fig 22 7 and 8) The suture is now tied and cut. The suture produces hemostatic and air tight closure (Fig 22 9)

A 14 F catheter is placed in the pleural space and the wound closed by suturing the intercostal muscles with 00 silk approximating the pectoral muscles and again suturing the skin Because of the constant positive pressure anesthesia there is no necessity for removal of air however 5 cc saline solution containing 100 000 units of penicillin is instilled into the pleural space and the catheter withdrawn No postoperative drainage is used The patient is allowed out of bed on the day of operation and is usually discharged on the third postoperative day

In the 50 patients no *dissemination* of the lesion and no pleural or wound infection occurred Postoperative roentgen studies proved the absence of hemothorax and pneumothorax Transient subcutaneous emphysema of minimal degree developed in two patients with pneumoconiosis and compensatory emphysema The biopsy site was examined at autopsy in one patient with extensive metastatic melanoma it showed excellent repair Biopsy of diffuse pulmonary lesions has permitted a rapid accurate diagnosis of such conditions as tuberculosis histoplasmosis pneumoconiosis and sarcoidosis as well as primary and metastatic carcinoma of the lung when the conventional methods failed to establish the true nature of the disease process

[The pressing need for direct biopsy of diffuse pulmonary lesions does not arise often As a rule other simpler diagnostic procedures give the answer When surgical biopsy is properly carried out as suggested the danger is not great yet cannot be considered negligible In some cases biopsy is mandatory —Ed]

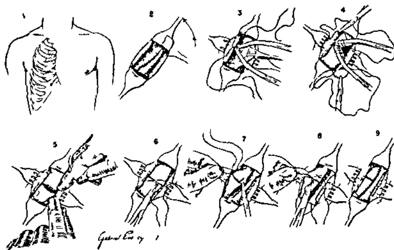
Resuscitation from Obstructive Asphyxia is reported by H Schwerma A C Ivy W L Burkhardt and A F Thometz (Chicago) Under local anesthesia tracheal obstruction was established in 103 dogs Various methods of treatment

(2a) Am. J Phy ol 156 145 148 February 1949

by use of a simple technic of pulmonary biopsy No serious complications developed and discomfort to patients was minimal

TECHNIC —Cyclopropane oxygen anesthesia is delivered under positive pressure with a face mask Since the biopsy specimen is taken from the inferior border of a lobe an anterior incision in the third or fourth intercostal space on the right is most advantageous this approach giving access to the inferior margin of the upper middle and lower lobes

After routine preparation of the skin with the patient supine an 8 cm incision is made over the fourth anterior intercostal space be



F g 22—T h of p lmo y b p y (Cou t y f Kla en K P *et l* A ch S g 59 694 04 Sept be 1949)

ginning 4 cm from the lateral border of the body of the sternum (Fig 22 *1*) In women the incision is made submammary, and upward retraction of the breast is used to expose the third or fourth intercostal space After separation of the fibers of the pectoralis major and minor muscles the intercostal space is exposed and the intercostal muscles cut midway between the rib margins The blades of a medium sized *Richardson* retractor are inserted parallel with the ribs into the incision and when the handles are rotated 90 degrees outward spreading of the ribs occurs with adequate exposure of the interlobar fissure (Fig 22 2)

With slight increase in intrabronchial pressure by the anesthetist the lower margins of the upper middle or lower lobes will herniate through the incision A small Duval lung clamp is used to grasp the edge of the lobe at the proposed site of biopsy A mattress suture of 000 chromic surgical gut with a swaged curved needle at each end

present practice these factors are not yet sufficiently understood to permit critical and quantitative assessment of the properties of the vaccine As measured by direct count or by dry weight of bacillary bodies the vaccines currently distributed in this country and abroad contain 1 5 billion bacterial cells per cubic centimeter of fluid Viability tests reveal however that only a fraction of a per cent of these cells are viable at the time of injection In view of this fact the general practice of giving directions in terms of cubic centimeters or milligrams of vaccine is meaningless and perhaps dangerously misleading The ability of all bacteria not excepting the tubercle bacillus to multiply in the animal body depends not only on size of the viable infective dose but also on the physiologic state of the bacterial cells The conventional technics used in cultivation and distribution of BCG vaccine expose the bacilli to such a variety of chemical and physical trauma that any vaccine preparation consists of an unpredictable mixture of cells possessing all degrees of physiologic age and activity

In addition the intrinsic virulence of a culture is one determinant of the extent to which it multiplies in susceptible animals Any statement concerning the virulence of a culture should be qualified by specifying not only the species and the breed but also the physiologic state of the animal used for the test Probably some of the conflicting reports concerning virulence of BCG for guinea pigs reflect differences in physiologic state of animals used by the various investigators

Any immunization procedure must be standardized in terms of the specific goal for which it is used It is highly desirable therefore that BCG preparations be standardized in terms of their ability to induce immunity against tuberculous infection There is as yet no well defined technic for such an assay Most tests aimed at evaluating the immunizing efficacy of BCG have been carried out by injecting into guinea pigs or cattle amounts of vaccine far greater than those used in human vaccination Immunization tests carried out under such conditions do not reflect the immunizing efficacy of the vaccine as used for immunization of man

Of extreme importance also is the technic employed in the challenge infection used to assay the resistance of the immunized animal When tubercle bacilli are injected into immunized guinea pigs they elicit the complex allergic reac

were instituted when the first terminal gasp occurred In previous experiments on carbon monoxide asphyxia this corresponded with a mean blood pressure of 42 mm Hg

In 22 dogs the tracheal obstruction was removed 32 per cent survived Manual artificial respiration in air was given 20 dogs 35 per cent survived When mechanical artificial respiration in air was used 75 per cent of 20 dogs survived With mechanical artificial respiration and 100 per cent oxygen 71 per cent of 21 dogs survived When mechanical artificial respiration with a mixture of 7 per cent carbon dioxide and 93 per cent oxygen was used 85 per cent of 20 dogs survived

The large minute volume of ventilation produced by artificial respiration accounts for its greater effectiveness in resuscitation The type of gas used produced no significant difference in results

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TUBERCULOSIS

Immunologic Aspects of BCG Vaccination are discussed by Rene J Dubos[4] There have been endless controversies *concerning the dangers and effectiveness of immunization* with BCG vaccine but little has been written concerning the immunologic basis and technical problems involved in preparation of the vaccine or measurement of its protective efficacy

BCG vaccine is a suspension of living tubercle bacilli obtained from cultures of a strain so attenuated as to be incapable of causing progressive disease in experimental animals It is almost certain that the immunity produced by the vaccine is the outcome of a limited but definite multiplication of the attenuated bacilli in the body of the animal undergoing immunization The degree of immunization probably reflects in a certain measure the extent of this multiplication and the degree of multiplication depends on at least four independent factors number of organisms injected their physiologic state their level of virulence and susceptibility of the *immunized* individual

As far as can be judged from published data and from

(4) Am. Re T be c. *60 670 674 No mber 1949*

to devise any laboratory test that would control the effectiveness of BCG vaccination Nevertheless BCG is the only immunizing agent for which there is enough experience to warrant administration to human beings and the urgency of the practical problems of tuberculosis may compel its use even though so much is ignored of its immunologic properties Analysis of the various factors which control the efficacy of immunologic procedures and development of technics which can be quantitatively evaluated would seem to be the responsibility of those who advocate widespread use of BCG as an immunizing agent

[This intelligent and critical analysis provides the physician with an excellent orientation with respect to tuberculosis vaccination. The peculiar problems of tuberculosis set it apart from the general run of infectious diseases in which prevention by vaccination is relatively simple and efficient.—Ed]

Tuberculosis in BCG Vaccinated Nurses Janet Kinney[4] (Chicago) presents case reports of two student nurses in whom tuberculosis developed 27 and 28 months after vaccination with BCG Both had experienced heavy exposure on tuberculosis wards Explosive onsets occurred four and six weeks after exposure

Clinically the first patient ran a hectic temperature with minimal nodal involvement and the second had a low grade fever with rather extensive parenchymal and nodal involvement Both showed little general reaction They ate well slept well felt well and had no complaints other than impatience with bed rest In both lymph node involvement was predominant but at the end of the second year one of the patients had no calcification The disease in these patients did not resemble the reinfection type of tuberculosis seen among unvaccinated persons This suggests that BCG has modified the course of the tuberculous infection

The difficulty in diagnosis is emphasized for in one patient the correct diagnosis was not made for a year

[Tuberculosis in BCG vaccinated persons may be due to failure of the vaccination to take to a natural infection which occurred before the vaccine was administered (a positive tuberculin test may not be elicited until six or eight weeks after infection) or to an exogenous superinfection The immunity conferred by BCG is not complete and its level varies furthermore it seems to be only temporary and probably is of much shorter duration than that conferred by natural infection —Ed]

(4) A I s Med 32 673 681 Ap 1950

tion known as the Koch phenomenon Possibly the resulting shedding or walling off by the vaccinated guinea pigs of some of the injected bacilli has its counterpart in human infection But even then it is probable that many of the bacilli are distributed throughout human tissues instead of being discharged outside the body Thus the Koch phenomenon which results in some protection of the vaccinated guinea pigs against artificial infection may fail to have a corresponding protective effect under the usual conditions of the human disease Fortunately there are many facts that suggest the existence of an antituberculous immunity completely independent in its mechanism from tuberculin allergy Much additional work is therefore required toward formulation of technics for evaluating the effectiveness of BCG as an immunizing agent under conditions that would reflect the processes at work in the human body

In the final analysis the usefulness of BCG immunization must be measured by its ability to protect human beings and cattle against tuberculosis The development of a positive tuberculin test is universally used as a criterion that the vaccine has taken but unfortunately the relation of tuberculin allergy to immunity is one of the obscure aspects of the pathogenesis of tuberculosis It is possible to render animals tuberculin positive by injecting dead tubercle bacilli into them without increasing thereby their resistance to infection Under certain conditions injection of BCG may also bring about a state of allergy without inducing immunity

It must not be forgotten moreover that an individual s response to an immunizing procedure is greatly affected by his physiologic state It is even possible that many of the classes of human beings who are most dangerously exposed to tuberculosis (for example those living under conditions of great economic stress with inadequate food supplies) may be those least capable of responding satisfactorily to immunization procedures For all these reasons it is urgent that technics be developed for measurement of true immunity (not tuberculin allergy) in order that BCG immunization programs can be intelligently controlled

Since the immunologic mechanisms which bring about immunity to tuberculosis are unknown it is not yet possible

killed tubercle bacilli of both virulent and avirulent variants showed essentially the same effect on leukocyte migration as the living bacteria

Control experiments were made to study the effect of charcoal India ink and two strains of staphylococci on leukocyte migration Phagocytized charcoal and India ink particles had no effect on the migration On the other hand one freshly isolated strain of Staphylococcus aureus was highly inhibitory whereas an old laboratory strain was not

Since virulent tubercle bacilli inhibit leukocyte migration whereas avirulent bacilli do not it is likely that the inhibition is in some way connected with the virulence of the bacilli On the other hand when a large number of avirulent tubercle bacilli are phagocytized a slight inhibition results suggesting that the difference between virulent and avirulent cultures might be quantitative rather than qualitative Since heat killed virulent and avirulent tubercle bacilli had the same effect on migration as living ones this action seems to be caused by a cellular constituent of the virulent bacilli and does not directly depend on their multiplication

[This fundamental study of virulence is one of the new approaches to a rather obscure problem Heretofore there have been no satisfactory measures of difference in virulence and it has been assumed that this factor played little or no part in human disease The more precise modern methods promise to help settle this question—Ed]

Effect of Tubercle Bacilli on Polymorphonuclear Leukocytes of Normal Animals Samuel P Martin Cynthia H Pierce Gardner Middlebrook and Rene J Dubos[6a] (Rockefeller Inst for Med Research) determined the comparative activity of virulent human tubercle bacilli of H37Rv and avirulent organisms of H37Ra strains in inhibiting the migration of guinea pig blood leukocytes by adding different amounts of these cultures to specially prepared microscopic slide cells There was no inhibition of leukocyte migration when the avirulent organisms were diluted beyond 1 10 Inhibition of migration could be detected with dilutions of virulent organisms as high as 1 80 Dilutions of 1 320 of the virulent cultures caused a slight stimulation of leukocyte migration

Migration of chicken leukocytes was inhibited by high dilutions of avian tubercle bacilli isolated from the viscera of

(6a) J Exp M d 91 381 392 Ap 1 1950

Vaccination with Murine Type of Tubercle Bacillus (Vole Bacillus) Since it has been shown that the murine type of tubercle bacillus does not produce progressive disease when injected either under or into the skin even in doses very much greater than are needed to produce a lasting sensitivity to tuberculin A Q Wells[5] (Med Research Council) conducted a vaccination experiment under conditions in which progress could be watched constantly Subjects were nonreactors to old tuberculin 81 of whom were vaccinated and 91 of whom were not During the observation period only one case of tuberculosis developed in the vaccinated group but among the unvaccinated there were four deaths from tuberculosis confirmed by autopsy and four additional cases of tuberculosis Under the conditions of the experiment the vaccinated and control groups were comparable as regards age sex conditions of life and degree of exposure and the persons to be vaccinated were chosen at random The vaccinated group showed a statistically significant resistance to infection compared with the control group

Effect of Tubercle Bacilli on Migration of Phagocytes in Vitro Martin Allgower and Hubert Bloch[6] (Basel Switzerland) describe a method suitable for studying the migration of polymorphonuclear leukocytes in vitro When leukocytes were allowed to phagocytize virulent tubercle bacilli before being implanted their migration was inhibited The degree of inhibitory effect depended on the ratio of bacteria to phagocytes In preparations in which owing to the small number of bacilli only part of the leukocytes had a chance to phagocytize bacilli a slight migration still occurred It could be seen however that all the leukocytes which contained bacilli did not leave the center of the preparation and that all the leukocytes in the surrounding halo were free from bacilli With a higher number of bacteria inhibition was complete

In contrast to the effect of virulent bacilli the avirulent variant did not inhibit migration Slight inhibition occurred only if a very high number of avirulent bacilli were added to the cell suspension so that almost all the phagocytes contained many micro organisms Rate of phagocytosis was the same with avirulent and virulent bacilli Phagocytized heat

(5) Lan t 2 53 55 J ly 9 1949
(6) Am Rev T berc. 59 562 566 May 1949

develops with much greater regularity and usually persists longer There is good general agreement among observers that a substantial majority of patients with sarcoidosis have a negative tuberculin test Those who adhere to the theory of tuberculous etiology of sarcoidosis have referred to this fact as evidence of a positive anergy implying that the patient is desensitized by the infected organism or its products Since *there is no known effect of circulating antibodies on the state* of tuberculin sensitivity it might be anticipated that anti bodies to the bacillus would still be present in the circulating blood of the sarcoid patient even in the absence of skin sensi tivity if the disease were indeed due to this agent The results of this study indicate that this anticipation is not realized Patients with sarcoidosis infrequently have circulating anti bodies demonstrable by complement fixation tests and those who do have antibodies tend to have a lower titer than pa tients with active tuberculosis

The question remains as to the significance of antibodies to Myco tuberculosis in the few sarcoid patients in whom they were found The authors believe that the positive com plement fixation reactions in these patients may be due to a past tuberculous infection unrelated to the sarcoidosis Unless patients with sarcoidosis have an impaired ability to develop complement fixing antibodies to the tubercle bacillus the con siderable difference in serologic reactions between them and patients with active tuberculosis indicates a difference in the etiology of these diseases

[Studies of this kind are welcome since they help to draw finer di tinctions wh ch eventually may lead to identification of the causes of sarcoidosis —Ed]

Laryngeal vs Gastric Cultures in Detection of Tubercle Bacilli M Duggan and Laura Delamater[8] (Brandon Man) state that the laryngeal swab method is a pleasanter and easier procedure than gastric lavage

METHOD —Laryngeal swabs are fashioned by making a small hook on which cotton wool is firmly tied on the end of a wire about 11 in long About 1 4 in from the swab end the wire is curved to a 90 degree angle The swabs are wrapped separately in brown paper and sterilized in a dry oven

The patient is seated opposite the operator who is suitably pro tected by a mask and a bronchoscopic glass headshield The patient s *tongue is held forward in a gauze strip by the operator s left hand*

(8) C d M A J 6 54 56 J y 1950

an infected chicken Migration was unaffected by an avirulent avian culture and only a little by a culture of the virulent human strain H37Rv The migration of guinea pig leukocytes remained normal in the presence of avian bacilli virulent or avirulent but was inhibited by the human culture Apparently specificity of inhibition of migration reflects the specific pathogenicity of the bacterial agent for the animal species from which the leukocytes are derived

Tests failed to disclose that the inhibition of leukocytic migration resulted from any gross damage caused by the bacilli to the leukocytes

Comparison of Sarcoidosis and Tuberculosis with Respect *to Complement Fixation with Antigens Derived from Tu*bercle Bacillus William H Carnes and Sidney Raffel[7] (Stanford Univ) performed complement fixation reactions on the serums of 22 patients with sarcoidosis using a variety of antigens prepared from the H37 strain of Mycobacterium tuberculosis There was no clinical or pathologic evidence of active tuberculosis among these patients and only four of them had positive tuberculin tests Positive serologic reactions were obtained on 5 (27 3 per cent) whereas 16 (61 7 per cent) of 26 patients with active tuberculosis gave positive serologic reactions and average titer was higher than in sarcoidosis Ten (33 3 per cent) of 30 healthy control subjects with positive tuberculin tests gave positive complement fixation reactions with a range of titers similar to that of patients with sarcoidosis

The authors experience indicates that complement fixation reactions with antigens of Myco tuberculosis are specific for tuberculosis No positive reactions were obtained in a group of healthy subjects with negative tuberculin skin tests negative histories and negative x ray examinations The considerable number of negative complement fixation tests on patients with active tuberculosis indicates however that detectable levels of circulating antibody may not always develop or persist during and after the infection

There is no established relationship between skin sensitivity to tuberculin and the presence of circulating antibodies to the tubercle bacillus Each develops in response to tuberculous infection and each may wane with time Skin sensitivity

(7) B ll J h H pk H p 85 04 2 0 S pt mbe 1949

Of the 206 specimens 29 (14 per cent) yielded positive cultures Fifteen of these were taken with the large tube and 14 with the small tube Though the number of colonies in each culture was recorded no conclusions could be drawn regarding the effectiveness of either tube in relation to the number of colonies per culture

In each series of four gastric lavages only one guinea pig was used In six cases the guinea pigs yielded positive results when cultures were negative In three however the cultures on a subsequent day were positive In the remaining three cases 16 negative cultures and 1 positive animal inoculation were obtained from four specimens Nine patients had specimens positive for tubercle bacilli on culture although negative on guinea pig inoculation however more specimens were cultured than were tested by inoculation

Twenty two of the 53 patients had sputum positive for tubercle bacilli Classification according to the roentgen findings revealed that 11 of the 53 had far advanced tuberculosis *A positive bacterial diagnosis was made on all these cases* In 7 of 11 patients with moderately advanced tuberculosis a positive bacteriologic diagnosis was made For 13 of the 28 patients with minimal disease cultures and guinea pig inoculations from gastric washings or additional sputum studies showed Myco tuberculosis

Specimens from 30 patients were divided into three portions one prepared immediately and cultured and the others kept 24 and 48 hours before culture Eleven cultures of those prepared immediately 6 of those kept 24 hours and 5 of those kept 48 hours were positive

The authors conclude that size of the tube used in collecting specimens is of no consequence Length of time between collection and culture is of great importance the shorter the time the greater being the chance of success Smears made of gastric contents are unreliable whether positive or negative for acid fast bacilli More positive cases will be found if repeated gastric washings are studied Both guinea pig inoculation and cultures should be used in the search for tubercle bacilli in gastric washings

[It is a good thing to have this precise study of an everyday procedure the efficacy of which is taken for granted. However in routine practice there are many errors which if avoided would improve the

and the swab dipped in sterile water slipped back over the tongue behind the glottis and down into the larynx The patient invariably coughs explosively onto the swab as it is quickly scraped over and around the cords The swab is withdrawn and after the wire is straightened manually with sterile gauze it is placed in a sterile tube.

The tube is filled with 6 per cent sulfuric acid and allowed to stand 10 minutes Then the acid is drained off and 1 2 cc of 5 per cent sodium hydroxide added After 30 seconds the tube is filled with sterile water to which a trace of methyl red has been added Drop by drop 5 per cent sodium hydroxide is added until the solution is neutral or lightly alkaline The swab is now left in the solution five minutes carefully rubbed over Petragnani medium and incubated for eight weeks

Of 100 patient 27 showed positive results with both gastric culture and laryngeal swab 5 with laryngeal swab only and 3 with gastric culture only

[This method of obtaining specimens for culture should prove expeditious and useful in many clinics The technic might be combined with the slide culture method for relatively quick results See this YEAR BOOK p 198—Ed]

Evaluation of Method of Obtaining Gastric Washings James B Holloway Jr and Martin Cummings[9] (U S Pub Health Service) studied the effect of certain variable factors in obtaining and examining gastric washings Fifty three consecutive patients whose sputum had been previously negative for tubercle bacilli were studied On four consecutive days lavages were performed a large caliber and a small caliber tube being used on alternate days Use of the large tube is based on the assumption that the tubercle bacilli are held in the thick mucous secretions of the stomach and deeply embedded in the rugal folds The small Levin tube with suction applied does not dislodge these bacilli During the 4 day examination period simultaneous 24 hour concentrated sputum specimens were examined

The smears from the gastric specimens were carefully studied a minimum of 30 minutes being spent on each smear Of 200 gastric washings from the 53 patients only 17 smears (14 patients) positive for acid fast bacilli were obtained In 6 of the 14 patients culture and guinea pig inoculation with that particular washing were negative for tubercle bacilli although 4 of the 6 had positive cultures on subsequent examination Therefore presence of acid fast bacilli on direct examination of the smear was of value in only two cases

(9) Am Rev Tuber 60 2 8234 Aug 1949

plug when the tube is horizontal A piece of ordinary glass tubing may be placed in the indentation to keep the tube from rolling In the horizontal position there is maximal opportunity for oxygen diffusion since the entire sputum film is only slightly beneath the surface of the medium and a large surface of liquid is exposed to air Cotton plugs are placed in glass cylinders of the same diameter as the tubes and placed in the autoclave When the medium is placed in the tubes the plugs are transferred to them The plugs are not sterilized in the culture tubes because of the inhibitory effect of distillate from the cotton on the growth of the organisms

On the second fourth and sixth days of incubation two cultures are taken out The slides are removed from the tubes allowed to dry fixed with heat labeled stained by the Ziehl Neelsen technic and examined under the microscope

Growth was present in 89 7 per cent of 26 two day cultures 82 4 per cent of 28 four day cultures and 100 per cent of 25 six day cultures Because of the characteristic morphology of the colonies (Fig 23) they are easily identified At the start of work with this method it is advisable to culture a strongly positive sputum so as to become familiar with the appearance of the colonies

[If facilities are available and the work is done by interested technicians this method should prove to be a means of expediting cultural study which is an extremely important phase of diagnosis In view of its importance for the tuberculous patient as well as for differentiation of nontuberculous diseases the expense and time required for precise bacteriology is well justified —Ed]

Mixed Infection of Hemolytic Streptococci in Cases of Primary Tuberculosis in Children. Publications dealing with antistreptolysin titer (AST) in healthy subjects both children and adults show varying figures for the frequency of pathologically raised titers From 3 to 16 per cent of healthy persons have been reported to show an AST over 200 (the normal limit generally agreed on)

Among 43 children with primary tuberculosis in the initial fever stage Sven Ivar Rollof[2] (Stockholm) found 11 with Streptococcus hemolyticus in the pharynx Of 51 children with primary tuberculosis in which the process was not over three months old but past the initial stage 15 had Str hemolyticus in the pharynx Of 54 with a process older than three months 15 had Str hemolyticus in pharyngeal smears Of 42 with primary tuberculosis which had originated with onset of erythema nodosum 21 showed Str hemolyticus Among 130 children from these four groups examined for AST about

(2) Ped tri 4 412 417 Oct be 1949

efficiency of this method and cause the patient a minimum of discomfort. —Ed]

Slide Culture Method for Early Detection and Observation of Growth of Tubercle Bacillus Preliminary Report J W Berry and Hope Lowry[1] (Univ of Colorado) describe a simple method by which Mycobacterium tuberculosis can be cultivated directly from sputum on slides and growth detected in one to six days

METHOD —From a specimen of sputum six smears somewhat thicker than those ordinarily used for microscopic examination are

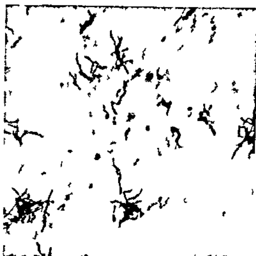


Fig 23 —Two day lt (6 × 90) Z hl Neel en t n Sm ll l s a ble o th b kg nd f th p t m film (Courtesy of B ry J W nd Low) H Am Re T be 60 51 61 July 1949)

prepared on new glass slides of the usual size After they have dried they are put in a glass rack which is placed in a covered stain dish and submerged in 6 per cent sulfuric acid for 20 minutes To remove the acid the rack is then transferred by aseptic technic successively to three similar dishes filled with sterile water the slides remaining in each 10 minutes Each slide is then placed in a special tube containing 20 cc. Kirchner s solution of electrolyte glycerol and asparagin with 0 5 per cent serum albumin and the tube is placed horizontally in an incubator at 37 C

The special tubes are 180 mm long with an inside diameter of 35 mm There is an indentation 20 mm in depth 110 mm from the closed end which prevents the medium from reaching the cotton

(1) Am. Rev T b r 60 51 61 July 1949

roentgenogram on Jan 31 1948 was negative However on Febru ary 4 21 days after inoculation a chest film revealed generalized miliary infiltration throughout both lungs At this time streptomycin therapy was instituted

Repeated blood cultures were negative Guinea pig inoculation of the patient s blood urine and cerebrospinal fluid gave negative results Temperature remained elevated until February 24 at which time the puncture wound in the left antecubital fossa opened and discharged thick pus After this temperature dropped to 100 F and seven days later fell to 99 F A chest film on the sixty fifth day of treatment showed definite improvement in the lung lesions The pa tient was di charged to her home 125 days after hospitalization and symptom did not recur after ce sation of therapy She had received 241 Gm. streptomycin in 105 days

[This unusual experience helps to provide clinical knowledge regard ing disseminated tuberculosis after blood tream infection Pulmonary lesions must attain a fair ize before they show in the roentgenogram Before this time there may be fleeting catarrhal rales which are the first local signs Fa lure to recover tubercle bacilli in blood cultures is also of special interest Apparently the organisms are picked up quickly by phago cytes and immobilized in the ti ue Hence unless there is a focus which acts as a con tant feeder the organi m will not be found and they sel dom are —Ed]

Disposition and Follow up of Pulmonary Tuberculosis Haynes Harold Fellows John A Evans and Margaret G Stephens[5] (New York City) present a study based on the character and extent of the lesion seen on the initial roent genogram Their conclusions are based on observations made on employees of the Metropolitan Life Insurance Company and on applicants for life insurance The employee group con sisted of 592 persons in whom lung lesions were discovered under a program of tuberculosis detection and control None had a history of tuberculosis 99 had had a previous roent gen examination considered negative and 493 had had no previous chest film After detection all were followed for 1 20 years The factors studied included character and extent of the initial lesion physical signs symptoms weight sex age and disposition at time of diagnosis Follow up observa tions included interval changes in roentgen appearance status of the employee (i e whether at work or able to work under going treatment or dead) continued or subsequent signs symptoms or changes in weight and surgical procedures for tuberculosis The life insurance applicant group consisted of 746 persons for whom roentgenograms were studied and classified and follow ups made

(5) Am R T be c. 60 487 500 O t be 1949

50 per cent had titers over 200 and over 67 per cent of patients with erythema nodosum had AST titers over 200

Results of this investigation indicate that mixed infection with hemolytic streptococci is widespread even in children with primary tuberculosis and that cases which start with erythema nodosum hold a special position with a high frequency of streptococcic infections As a consequence of these findings Rollof gives penicillin for about one week to patients with primary tuberculosis who have either spontaneous erythema nodosum or a high antistreptolysin or antistaphylolysin titer

[It would be interesting to carry out a similar study in the United States where the occurrence of erythema nodosum in the primary phase of tuberculosis appears to be much less common than it is in the Scandinavian countries for instance —Ed]

Miliary Tuberculosis Caused by Intravenous Self injection of Tubercle Bacilli, Treated Successfully with Streptomycin Therapy is reported by Oswald R Jones Warren D Platt and Luis A Amill[3] (St Luke s Hosp New York City)

Woman 30 injected into herself intravenously 1 cc of suspension of a *virulent strain of tubercle bacilli with possible suicidal in*



Fig 24—Tuberculous lesion at site of venipuncture in left arm (Courtesy of Jones O R et al Am Rev Tuberc 60 514 519 October 1949)

tent. Three years previously she had accidently inoculated herself in the skin of the left antecubital fossa with a needle contaminated with tubercle bacilli Thereafter a small superficial papule developed which disappeared after a few weeks

An initial fever of 48 hours duration developed after the intravenous injection Nine days after the injection chills and fever again developed A small red tender raised area appeared in the left antecubital fossa (Fig 24) at the site of venipuncture on the day after the injection After six days of spiking temperature a chest

(3) Am Rev Tuberc 60 514 519 October 1949

cal observation and periodic roentgen examinations throughout life.

[Perhaps the greatest difficulty is in determining the pathologic character of small lesions which in the roentgenogram may appear quite discrete, simulating fibrosis. In young persons particularly these small *lesions are usually progressive sometimes acutely unless they are* promptly and carefully treated.—Ed.]

Tuberculosis Mortality in United States, 1948, was studied by Lillian Guralnick and Stanley Glaser.[3a] The trend of

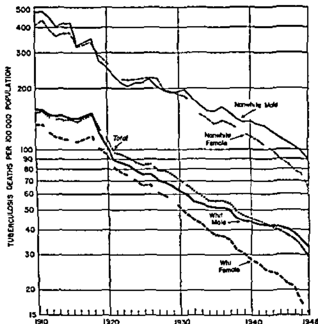


Fig 25.—D th te for t be cul s (ll f rm) by and sex (d th g tr ti tat) 1910 48 R te f 1940 48 mput d from d th e l d g those m g rmed for se d p p l t on l d g rmed f o s (Cou t y f G l k L d Gl S P b Health R p 65 468 493 Ap 1950)

the total death rate from tuberculosis for the United States during 1910-48 and of the rate for the four race sex groups is shown in Figure 25. There were 43 833 deaths from all *forms* of tuberculosis in the United States in *1948*. The rate was 30/100 000 population in comparison with a rate of 33.5 for 1947. The rates for females continue to fall faster than

(3a) P b. Health R p 65 468-493 Apr 7 1950

After analyzing the results of this carefully planned long range follow up the authors believe that it is possible to adopt a practical program of classification and disposition based on the original roentgen examination A satisfactory tuberculosis detection and control program may be instituted with safety for the individual patient if he is followed up carefully and with advantage to the community which can plan to use available treatment facilities

The authors classification of lesions by roentgenogram comprises three groups inactive questionably active and active In the inactive group the roentgen appearance is that of fine or coarse strands small or large calcific densities and small opaque areas with clearly outlined borders These lesions may be localized or scattered the extent being minimal or borderline moderately advanced (National Tuberculosis Association) It is recommended that this group continue at work under careful supervision and with periodic roentgen examination throughout life

In the questionably active group the roentgen appearance may be (1) areas having the general characteristics described earlier but tending toward softness the extent being extensive minimal or moderately advanced (N T A) (2) areas of cloudy mottling or homogeneous densities with hazy or not clearly defined borders and no suggestion of cavity The extent is minimal or borderline moderately advanced (N T A) It is recommended that this group be placed under observation as soon as possible preferably in a sanatorium for about three months Medical action includes careful study with serial roentgenograms and repeated sputum examinations instruction in treatment and control of tuberculosis and eventual classsification as either inactive or active

Active lesions may present roentgenographically as (1) extent far advanced (N T A) (2) moderately advanced with hazy borders or cavitation of less than 4 cm (3) any shadow regardless of extent or character developing after a film interpreted as normal or average Patients in this group should be placed in a hospital or sanatorium at once and treated as having active tuberculosis

As a result of the observations and experience in the present study the authors are convinced that all patients with lesions which may be of tuberculous origin should have medi

range from 58 and 76 3 for Japanese and Negroes to 143 2 and 166 7 for Indians and Chinese

Of the total deaths from tuberculosis in 1948 92 2 per cent were from tuberculosis of the respiratory system and 7 8 per cent from nonrespiratory forms of the disease The rate for tuberculosis of the respiratory system was 27 7 and for all other forms 2 3 The death rates for tuberculosis (all forms) by state of residence (Fig 26) ranged from 9 5 for Iowa to 82 4 for Arizona

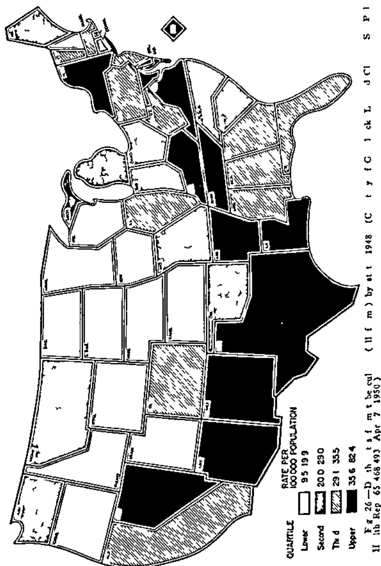
During the last 21 years the largest relative declines in deaths from tuberculosis of the respiratory system have occurred among children Smaller declines have taken place up to age 65 Beyond this age small but consistent increases are apparent in the death rates for both white and nonwhite males beginning with 1941 but the rates for females over 65 have continued to decline

[The decline in tuberculosis mortality in the United States places us in the most favored position in the world in this respect. At the same time it should be realized that the prevalence of infection especially among adults remains high This implies a rising level of resistance against progressive disease a delicate balance which must be maintained if the favorable trend is to continue Also it is not to be forgotten that throughout the world tuberculosis is still the most serious of all infectious diseases —Ed.]

Problem of Tuberculosis Control among American Negroes is discussed by Howard M Payne[4] (Howard Univ) *The prevalence of tuberculosis among Negroes does not exceed that among whites to an extent comparable to the excess of mortality Among American Negroes tuberculosis is more* severe and more rapidly fatal than among whites The factor of race in the ethnic sense plays only a small part in identifying the Negro in the United States Cultural occupational economic and educational limitations set the nonwhite group apart A biologic explanation of the observed severity of tuberculosis in a group not biologically defined is illogical

Environmental conditions increase the severity with which tuberculosis strikes Number and severity of bacillary inocula are greater for a group which experiences to a greater extent than another the disadvantages of crowding unsanitary environment and social disorganization Hypersensitivity develops more strongly as a consequence of larger inocula with more bacilli Natural resistance depends on good nutrition and

(4) Am R v T be 60 332 342 Sept mbe 1949



F g 26 —D th t s f m t be cul (ll f m) by st t 1948 (C t y f G l ck L d Cl S P l H lth Rep 65 468 493 Apr 7 1950)

those for males The 1948 rates were 33 3 for white males 15 4 for white females 92 1 for nonwhite males and 65 4 for non white females The rates for the principal nonwhite groups

tients pleurisy was not associated with any visible parenchymal lesions whereas in the others it followed parenchymal disease The latter group included both initial reactors and nonreactors

Of the 54 patients with minimal tuberculosis 89 per cent are living a normal life with disease arrested The others had more extensive disease and include 10 in whom the process is finally arrested 3 still under treatment and 3 who died There were 24 instances of reactivation among all nurses with tuberculosis 20 occurring in those with minimal tuberculosis *Final rate for all lesions was 0 93/100 nurses/year* and rate for new pulmonary and pleural lesions needing treatment 0 73/100/year

The results of this survey do not support clinical differentiation into primary or childhood and reinfection or adult tuberculosis since the type of disease was essentially the same in character course and prognosis in both groups Most if not all the tuberculosis in these patients was primary first infection tuberculosis whether it appeared in the initial reactor or nonreactor to tuberculin In both groups infection went on to progressive destructive tuberculosis of almost any type or became rapidly arrested suggesting that allergy plays less part in the pathogenesis than inherent constitutional differences in resistance to tuberculosis together with environmental factors and treatment The individual inherent constitutional resistance to tuberculosis clinically seemed the most important single factor

[The important point of this study is that in young persons most pulmonary tuberculosis is in reality progressive primary disease The interval between acquisition of infection and progression of the lesion to the point where it may be diagnosed varies from months to many years In the latter event specific relative immunity may have developed to a considerable degree and this may be an asset during treatment.—Ed]

Contact Ulcers and Laryngeal Tuberculosis Though few autopsies with histologic examination of contact ulcers have been reported numerous biopsy reports on such ulcerations have been published Henrik Johansen and William Kiaer[7] (Copenhagen) have found that even when the entire suspected area is examined histologically at autopsy it is often necessary to make serial sections in order to demonstrate any tubercu

(7) A h Otol ry g 50 264 283 S pt mb 1949

age at first intensive exposure These two factors are demon strably unfavorable to maintenance of resistance in a large portion of the Negro minority Acquired resistance follows in oculation with tubercle bacilli in an optimal dose Massive or frequent inocula may cause hypersensitivity and on a purely mathematical basis may enable bacillary growth to outstrip development of acquired immunity This favors the develop ment of progressive tuberculosis These factors can be demon strated and do not require the invocation of race specific phe nomena as speculative influences

[There have been various explanations for the higher prevalence of severe and fatal tuberculosis among Negroes than among whites Gener ally speaking there is now less tendency to implicate the mass and fre quency of infection as the chief factor Instead greater emphasis is placed on the level of native resistance and its influence by the state of nutrition personal hygiene and environmental conditions —Ed]

Tuberculosis in Nurses Clinical Observations on Its Pathogenesis as Seen in 15 Year Follow up of 745 Nurses In the group studied by Theodore L Badger and L Fred Ayvazian[6] (Harvard Univ) tuberculosis developed in 71 nurses of whom 4 died Two had been initially negative and two positive reactors On entrance into training the tubercu lin negative and positive reactors were almost equally divided Although somewhat more tuberculosis appeared in the initial nonreactors in the observation period there was no statisti cally significant difference in total amount of disease appear ing in the two groups Rates at which tuberculosis appeared each year after entrance into training in the two groups of tuberculin reactors followed closely parallel courses In the initially negative reactors 55 per cent of the tuberculosis ap peared within two years after admission to training whereas 32 per cent appeared in the same period in initially positive reactors These values are to be compared with the 85 per cent of disease demonstrable in the initially negative two years after date of conversion of tuberculin tests to positive At the end of the first five years rate of appearance of tuberculosis in all three groups was similar

For the most part the lesions encountered were small pul monary infiltrations Pleurisy with effusion appeared in nine initially negative and in three positive reactors In four pa

(6) Am R v Tuberc 60 305 330 September 1949

[The diagnosis of laryngeal tuberculosis is not often difficult since this lesion rarely develops except in the presence of cavitary pulmonary tuberculosis Biopsy of tuberculous lesions is objectionable because of the possibility of aggravation If the presence of the pulmonary lesion is proved it is eldom necessary to explore furthe to identify the nature of the laryngeal condition —Ed]

↓ During the past year a large number of reports have appeared de scribing experiences with specific antimicrobic therapy of tuberculosis Most of these have related to the merits of different dosages and regimens of streptomycin the problem of development of bacterial resistance to the drug and the re ponse of different forms and phases of the disease to treatment Since large daily doses of streptomycin frequently prove toxic demonstration of the efficacy of doses in the range of 1 Gm a day is for tunate In some instances it appears that wider spacing of the dose at intervals of two or three days may prove adequate particularly when para aminosalicylic acid is also used This observation applies mainly to the milder and less acute forms of tuberculosi The combination of strep tomycin and para aminosalicylic acid is of particular interest because of the delayed demonstration of manifest bacterial resistanc to streptomy cin and the advantage of permitting administration of the two drugs over prolonged periods These factors may be helpful in many mildly ac ive and chronic cases in which slow stab lization of the disease resolution of inflammatory exudate and improvement of the patient s general condi tion may prepare the way for helpful surgical procedures which other wise would never have been possible The limitations of specific therapy are being more clearly recognized, and initial sati factory response may be followed by relapse This is particularly unfortunate if bacterial resistance to the drugs has developed rendering them useless Such po s bilities are now roughly calculated and a long plan of treatment is laid out o as to attain the maximal benefit of the drugs at the most st ategic time In this plan bed rest sanatorium care collapse therapy and surgery are all con idered In advanced cases the scope of surgery has been greatly widened through u e of drugs The late results in tuberculous meningitis especially when it is a complication of manifest generalized miliary tuber culo is are very disappointing however the superior experience in in fants and children may point the way to improvement as available drugs and newer ones are used in combination —Ed

Current Status of Chemotherapy of Tuberculosis in Man [8] The third annual progress report on a co operative investiga tion by the Veterans Administration Army and Navy is based on results obtained in treatment of about 7 000 patients with all types of tuberculosis by 22 different regimens By early 1947 the fact that streptomycin does produce a tuber culostatic effect in clinical tuberculosis had been demon strated However streptomycin can hardly ever be counted on to cure tuberculosis though it is the most potent chemo therapeutic weapon available *Streptomycin should be com bined* with other forms of therapy should not be given on an ambulatory basis and should not be administered to see what

(8) J A M A 142 650 653 Ma 4 1950

lous changes A negative result with regard to specific changes in the usually small pieces of tissue removed for biopsy is to be accepted only with reservation

During five years 21 patients with contact ulcer were stud ied Of 19 patients with severe pulmonary disease 17 had tuberculosis and 2 nontuberculous lesions of the lungs In 14 of the 17 patients with pulmonary tuberculosis the tuberculous nature of contact ulcers was established and in 2 it was very likely for the remaining patient the diagnosis was more du bious All 17 tuberculous patients had severe pulmonary le sions with masses of tubercle bacilli in the sputum Of these patients 15 were men

The ulcers of the vocal processes did not represent part of extensive ulcerative or proliferative tuberculosis of the larynx for in about two thirds of the cases the contact ulcer was the only demonstrable sign of laryngeal tuberculosis It seems probable that contact ulcer may be—and often is—the only manifestation of tuberculosis of the larynx

It is a striking fact that contact ulcer of the larynx occurs predominantly in men Laryngeal tuberculosis on the other hand occurs about equally in men and women Of the known contributing causes of contact ulcer the most important fac tor which may differ to some extent in men and women is inhalation of tobacco smoke which undoubtedly is more prevalent among men

In the pathogenesis of tuberculous contact ulcers the mechanical factor cannot be left out of consideration The morbid process may result from an initially unspecific contact ulcer which secondarily becomes infected from the bacilli containing sputum or the primary feature may consist of subepithelial elementary tubercles on the vocal processes subsequently ulcerating through the mucous membrane in re sponse to the traumatic influences

To elucidate whether ulcerations on the vocal processes are particularly frequent in debilitated persons with lowered resistance the larynx was thoroughly examined at 50 succes sive autopsies at the old people s home Two instances of con tact ulcer of the larynx were found In these old people all of whom had atherosclerosis often of extreme degree the lesions on the vocal processes are undoubtedly to be looked on as a sort of decubitus ulcer

Routine use of prophylactic chemotherapy in thoraco plasty is considered inadvisable because of the low incidence of spreads without it and the hazard of development of re sistant micro organisms In pulmonary excisions prophylactic chemotherapy has resulted in such a low incidence of spreads in comparison with control series that it should be continued In such cases development of resistant organisms has in creased but this may be a result of operation being performed in the face of greater risk or because of previous treatment with the drug

In equivalent daily dose of 1 Gm dihydrostreptomycin is somewhat inferior to streptomycin Although it may have less effect on vestibular nerve function when given in a dose of 2 Gm daily it may produce loss of hearing which has rarely been observed with streptomycin The chief value of dihydrostreptomycin is in patients unusually susceptible to the toxic manifestations or other sensitivity phenomena of streptomycin

The thiosemicarbazone TB1 698 appears definitely less effective than streptomycin exerting a tuberculostatic effect of the order of or perhaps greater than that of para amino salicylic acid (PAS) It may be more toxic than either drug in its tendency to produce liver damage and blood dyscrasias

Resistant tubercle bacilli have developed in 80 per cent of patients treated with streptomycin but not given PAS if cul tures are positive at the end of 120 days If PAS is used as well the incidence is reduced to 30 per cent However tubercle bacilli may become resistant to PAS Also its use may be accompanied by major skin eruptions or symptoms of gastro intestinal irritation grossly

Interrupted regimens under which 1 2 Gm streptomycin is given every third day for 120 days or daily for 4 weeks followed by a rest period of 4 or 6 weeks and then a repetition of the course have been tried Therapeutic efficacy of these regimens is surprisingly little decreased and delayed emer gence of resistance appears to have resulted Whether the incidence of resistance has been decreased is not established

Factors Influencing Outcome of Streptomycin Therapy of Pulmonary Tuberculosis are discussed by William B Tucker[9] (Univ of Minnesota) who reports experience in 86 cases

(9) D Ch t 16 714 743 D cembe 1949

it will do The treatment plan should be carefully worked out before therapy is started and the surgical staff consulted because of the likelihood of appearance of streptomycin resistant tubercle bacilli collapse or excisional therapy should be used early in streptomycin treatment

Resistance of the organism to the drug makes further treatment with streptomycin ineffective and makes the patient a source for the spread of a tuberculosis which though no more serious of itself has the disadvantage of being unresponsive to therapy with streptomycin Incidence of toxic manifestations from streptomycin can be significantly diminished by dosages of 1 Gm divided between two daily injections Development of resistance can be only partially avoided by decreasing the duration of treatment from 120 to 42 days and then only with a definite loss of therapeutic effectiveness

Lesions of mucous membranes of respiratory and alimentary tracts draining cutaneous sinuses with concomitant surgical treatment and peritonitis continue to respond most promptly and uniformly to streptomycin therapy with healing and considerable improvement in 80 90 per cent of cases In bone and joint tuberculosis improvement occurred more rapidly and to a somewhat greater extent in patients given streptomycin than in those who had no chemotherapy and surgery was possible which would have been impossible without the drug Cystoscopic and symptomatic improvement of genitourinary tuberculosis is observed in about 80 per cent of cases Genital lesions are not usually improved unless chemotherapy is accompanied by surgery Renal destruction demonstrated by pyelograms is infrequently benefited (20 per cent)

The first 100 cases of miliary and meningeal tuberculosis have been followed for an additional year and between two and three years after initiation of streptomycin therapy there are 21 survivors The survival rate in miliary tuberculosis is about 50 per cent but if this is accompanied or followed by meningitis it is zero In cases of pure meningitis the survival rate is about 15 per cent if chemotherapy is used Single intrathecal injections of streptomycin should not exceed 50 mg and may be omitted because of the increased permeability of the cerebrospinal fluid blood barrier which accompanies infection

per cent in unmixed cases and 78 per cent in mixed cases at the end of the first six month follow up Relapse rates at 10 and 22 months after the start of treatment were definitely higher in the mixed than in the unmixed cases Collapse therapy in unmixed cases resulted in more favorable results than if it had not been used

It is concluded that the response of the cavitary components to streptomycin therapy is the chief factor determining the outcome of a program of which streptomycin is a part Prompt application of collapse therapy usually during the first eight months after the start of antibiotics the period of maximal benefit from streptomycin presents the best method for improving still further results of streptomycin therapy of tuberculosis

Pulmonary Tuberculosis in Children Treated with Streptomycin Eugene T McEnery Henry C Sweany and George C Turner[1] (Chicago) report results in treatment of 21 patients Eighteen had a progressive primary lesion This type of lesion is of relatively recent origin sometimes demonstrated on physical examination by impaired percussion resonance and suppressed breath sounds but more often not revealed by physical signs Roentgenograms show a soft infiltrative process usually extending out from the hilus to the periphery of the lung with some enlargement of the hilar shadows Three patients had far advanced adult type pulmonary tuberculosis with activity and large cavities These children had failed to respond to bed rest and pneumothorax regimen and had been on a downward course for two years Most patients received streptomycin in 0 5 Gm daily doses at the beginning of the study Later this was reduced to 0 3 Gm daily Treatment was continued for 90 120 days

All patients appetites and general well being improved and temperature dropped within 7 10 days Later the physical findings also improved and roentgen changes decreased Conversion of sputum from positive to negative was completed in four to five months in 89 per cent of primary progressive lesions On the basis of clinical roentgen and bacteriologic observations it was demonstrated that degree of therapeutic efficacy of streptomycin is related to the type and stage of the

(1) P d t 4 323 330 S pt mbe 1949

In 32 old regimens were used At first a daily dose of 2 Gm was given for 120 days later patients were given 2 Gm daily for 60 days and then 1 Gm daily for 120 days New regimens were used in 25 cases—1 and 0 5 Gm daily for 42 days These 57 cases are designated as protocol cases In 29 non protocol cases active pulmonary tuberculosis was present but streptomycin was given primarily for extrapulmonary tuberculosis

To aid in evaluation of results each case was characterized as acute subacute or chronic inflammatory The cases fell quite easily into relatively unmixed stages of acute tuberculosis or into mixed categories which nearly always combined a definitely chronic component with either an acute or a subacute inflammatory component

Study of the protocol cases showed that there was slightly more far advanced disease and cavities demonstrable more often in the mixed than in the unmixed group There was considerable difference in clinical results between the two groups With respect to all degrees of x ray improvement the 35 unmixed cases showed 100 per cent improvement at 4 months 94 per cent at 10 months and 82 per cent at 22 months after the start of treatment The corresponding figures for the 22 mixed cases were 73 per cent at 4 months 50 per cent at 10 months and 40 per cent at 22 months There was a corresponding disparity in the relapse rates for the two groups at both 10 and 22 months after the start of therapy The sputum conversion rate was 60 per cent in the unmixed and 14 per cent in the mixed cases Mortality from pulmonary tuberculosis was 36 per cent at 10 months for the mixed group and 3 per cent at 10 months for the unmixed group Results were better in the unmixed protocol cases in which collapse therapy was used with streptomycin than in similar cases without collapse therapy

The 29 norprotocol cases were so different from the protocol cases that he effects of streptomycin were studied separately The disease in the 9 mixed cases was far more advanced more progressive more cavernous and more predominantly exudative than in the 20 unmixed cases Both groups showed about 90 per cent x ray improvement at the end of the four month treatment period but improvement was 100

course at first is similar to that of the untreated patient Even the comatose stage may develop and yet be followed by complete recovery

Promizole* is apparently less toxic when given in combination with streptomycin Cyanosis enlargement of the thyroid elevation of blood cholesterol content leukopenia or pink urine may occur The toxic reactions to streptomycin have been similar to those reported elsewhere

Streptomycin is contraindicated in forms of tuberculosis such as primary infections and minimal chronic pulmonary tuberculosis which usually respond without chemotherapy It should not be used in an attempt to prevent complications Streptomycin alone has been restricted to forms of tuberculosis which might be benefited or cured by treatment not exceeding six weeks In some of these cases temporary control of the disease permitted such procedures as surgery or collapse therapy which would have been contraindicated otherwise

Tuberculous laryngitis endobronchial tuberculosis and bronchogenic spread due to locally progressive primary tuberculosis have been treated successfully with streptomycin as the sole agent Moderate to far advanced pulmonary tuberculosis of the so called reinfection type in children has been treated with initial rapid improvement followed by diminution in extent of exudative lesions Streptomycin is best used in these cases as an adjunct to pneumothorax and other accepted methods of treatment

[The apparent superior results of treatment of meningitis in children over those in adults is not clearly explained Various possibilities have been suggested including the use of relatively larger doses of streptomycin, the combined administration of promizole* over prolonged periods earlier diagnosis than is usually made in adults or a better response to therapy Children seem to tolerate large doses of streptomycin much better than adults —Ed.]

Clinical Study of Toxic Effects of Dihydrostreptomycin and Streptomycin was made by Charles M Domon Phillip C Kilbourne and Ernest Q King[3] (Howard Univ) In most clinical studies with dihydrostreptomycin the amount of toxicity produced was compared with that which had been produced in the past with equivalent doses of streptomycin Current opinion about the effect on the vestibular apparatus of

(3) Am R T be 60 564 575 N mber 1949

pulmonary lesion Improvement occurred much more frequently in patients with early and acute disease processes than in those having late and chronic lesions

The three children with adult type pulmonary tuberculosis formed a group too small to be statistically significant but observations suggested that results were similar to those in adults with pulmonary tuberculosis treated with streptomycin Two patients improved only temporarily One died and the other has reached the terminal stage The third child is awaiting surgery

Chemotherapy of Tuberculosis in Children is discussed by Edith M Lincoln and Thomas W Kirmse[2] (Bellevue Hosp) In treatment of miliary tuberculosis and tuberculous meningitis it appears desirable to continue tuberculostatic action for long periods Streptomycin is unsuitable for prolonged therapy because of its potential toxicity and the tendency for tubercle bacilli to become resistant By using streptomycin and promizole® simultaneously advantage can be taken of the rapid action of streptomycin and therapy continued with the sulfone which can be given safely and effectively for years

The combined therapy was given 10 children with miliary tuberculosis Nine were given 1 Gm streptomycin daily intramuscularly for 120 days the other child received 0 4 Gm daily All were given promizole® orally four times daily in amounts sufficient to obtain a blood level of 1 3 mg/100 cc It is planned to continue promizole® administration for three years During this regimen two patients died one six days after therapy was begun the other died of tuberculous meningitis after recovery from miliary tuberculosis The others are well 6 23 months later No relapses have occurred

Of 18 patients with tuberculous meningitis 13 have survived 8 for more than a year So far the general behavior of all the survivors is well within normal limits For such patients intramuscular administration of streptomycin is continued for 180 days In addition 0 1 Gm is given once daily intrathecally until toxic symptoms or mechanical difficulties occur Thereafter it is given every two days but if toxic symptoms recur the dose may be reduced to 0 05 Gm and is given until a series of 40 treatments has been completed Usually there is no immediate response to therapy and the

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amounts of streptomycin (30 150 Gm) but in none of these four did the total amount of streptomycin received before and during the study exceed 200 Gm before vestibular damage occurred

Two other patients in the streptomycin group had been given the drug previously One of these has shown no measurable toxicity The other had been given 18 Gm streptomycin immediately before the study at the rate of 1 Gm daily and showed no definite toxicity until one week after completing the 270 Gm course of treatment He was the only patient in the streptomycin group with vestibular damage resulting from more than 200 Gm streptomycin whereas all nine patients in the dihydrostreptomycin group tolerated 270 Gm or more with no measurable vestibular damage

[There have been conflicting reports of deafness apparently caused by dihydro treptomycin which may become manifest early or a few months after cess tion of treatment By contrast it has been the general experience that dihydrostreptomycin affects the vestibular branch of the eighth cranial nerve consistently less than streptom cin in equivalent doses The quest on of deafness is being studied further since it is not clear whether excessive dosage or some other factor is responsible —Ed.]

Transmission of Streptomycin Resistant Tubercle Bacilli in Man A new and potentially serious problem of public health has been anticipated in view of the steadily increasing number of cases of pulmonary tuberculosis in which patients after treatment with streptomycin remain sputum positive with the tubercle bacilli highly resistant to streptomycin Animal experiments indicate that such resistance is probably permanent and that a tuberculous infection resistant to subsequent streptomycin therapy can be transmitted from one animal to another

Norma C Furtos and Edwin A Doane[4] report a case indicating that such transmission of streptomycin resistant tuberculosis can occur in man

Woman 36 a lieutenant of the Navy Nurse Corps was admitted to the sick list on June 28 1947 Her known exposure to tuberculosis began Aug 17 1946 when she was assigned to the Streptomycin Study Unit at United States Naval Hospital Sampson N Y during the cour e of which study many patients became highly resistant to streptomycin. Routine roentgenograms of the chest in August September and December 1946 revealed no evidence of pulmonary disease other than a small calcified nodule in the right third anterior

(4) J A M A 140 1274 1275 A g 20 1949

2 or 3 Gm streptomycin is based largely on the experience gained from 1945 to 1947 when these doses were widely used in treatment of tuberculosis The authors thought it desirable to test dihydrostreptomycin against currently produced streptomycin since the earlier observations of the toxic effects of large doses of streptomycin might not still apply When the damaging effects of these two drugs are compared in a small series it is necessary to use a high enough dose to produce a significant amount of toxicity with at least one of the drugs

Ten patients given streptomycin sulfate 3 Gm /day for a maximum of 90 days and nine given dihydrostreptomycin 3 Gm /day for 90 days were observed daily for toxic manifestations and caloric responses were tested weekly Because of the large doses of the drug being used treatment was stopped at the first definite sign of vestibular damage either subjective or objective unless the patient s need for and apparent response to treatment justified its continuation All patients had normal caloric response audiogram nonprotein nitrogen concentration in the blood and urinalysis before starting treatment All had normal hemograms except five with eosinophilia above 4 per cent two of whom were in the streptomycin treated group and three in the dihydrostreptomycin group

None of the patients given dihydrostreptomycin showed any signs or symptoms of toxicity during treatment or for seven weeks thereafter Eight streptomycin sulfate treated patients developed symptoms of vestibular damage and subsequently lost their caloric response though treatment was usually stopped shortly after onset of symptoms The remaining two streptomycin sulfate treated patients showed no signs of toxicity in any form The characteristic signs and symptoms of vestibular damage were always followed or accompanied by complete loss of caloric response whether treatment had been discontinued or not No significant hearing loss was noted in either group of patients during or after treatment

Of the eight patients in the streptomycin group in whom vestibular damage occurred seven showed definite evidence of this damage before the fifth week of treatment and before more than 100 Gm streptomycin had been given Four of these patients had previously been treated with varying

range reaching normal in 6-12 months or (3) reached normal in 4-6 weeks Blood count and hemoglobin level normalization paralleled that of temperature There was a gradual reduction in pulse rate which seemed to reflect most accurately the course of the disease Alterations in acid fast organisms included striations When many acid fast bacilli

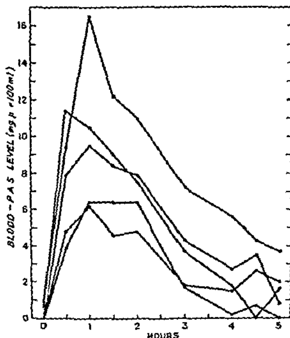


Fig 27—Blood PAS l l h pat ts g ngl dose f PAS 7 5 Gm By th d hou tw p ti ts h d blood PAS) k f les th 2 mg /100 ml (C te y f M d g D G et l Lancet 1 239 245 F b 11 1950)

were demonstrated in direct or concentrated smears adequately controlled culture methods yielded only sparse growth or none Nausea occurred in 32 patients and 22 had nausea diarrhea and vomiting Sensitization to the drug was observed in three patients Of 22 strains of tubercle bacilli isolated before therapy the range of sensitivity to PAS was 0 006-0 025 mg /100 ml in a Dubos and Davis medium inoculated with 0 01 mg /ml after seven days incubation *Strain H37Rv*

interspace On Mar 3 1947 a minimal lesion in the right supra clavicular region was noted

In April 1947 the patient began to lose weight and have a pro ductive cough and finally noted pain in the anterior region of the right lung On June 18 a roentgenogram revealed an increase in the previously observed lesion for which reason she was admitted to the sick list Sputum was negative for tubercle bacilli but a culture of gastric contents obtained on June 30 was highly positive and the bacteria grew readily in Dubos liquid mediums containing as much as 1 000 μg /cc streptomycin On July 3 a tuberculin reaction to the first strength of purified protein derivative was 2 plus

The authors have examined more than 385 patients for possible resistance to streptomycin before beginning a course of streptomycin therapy and in no other instance was initially high bacterial resistance detected except in patients who had previously been treated with streptomycin With a definite history of continuous exposure to bacterial resistance as in this case it is exceedingly likely that the infection was de rived from some such resistant source

[Incidental to this information it is noteworthy that tuberculous patients with positive sputum under treatment in hospitals where much streptomycin is used have not been found to cast off streptomycin resistant bacteria unless they themselves have received streptomycin treatment This would seem to imply that superinfection of patients harboring un healed tuberculous lesions does not occur frequently a concept supported by pathologic studies such as those of Medlar —Ed]

Para Aminosalicylic Acid in Tuberculosis Clinical and Pharmacologic Aspects are discussed by D G Madigan L L Griffiths M J G Lynch R A Bruce Sidney Kay and George Brownlee[5] (Farnborough Hosp Kent) It was found that a single dose of para aminosalicylic acid (PAS) 7 5 Gm is quickly absorbed produces a peak in the blood level in ½ 1 hour and is rapidly excreted in about 4 hours (Fig 27)

PAS alone was given 53 patients with pulmonary tuber culosis and in conjunction with other agents to 11 Some had bilateral tuberculosis others were being prepared for surgery and some had been treated with artificial pneumothorax for six months without complication When the temperature was high there was a rapid lysis to about 99 5 100 5 F in 48 72 hours If the temperature was already in this range the altera tion was less noticeable or absent Usually night sweats were immediately relieved Erythrocyte sedimentation rate (1) fell quickly to normal (2) fell from a very high to a lower

(5) Lan t 1 239 45 F b 11 1950

more clinical experience with PAS which will make it possible to correlate occurrence of tubercle bacilli resistant to the drug in vitro with response to therapy An approach to this question may be made by comparing response to treatment with PAS of animals inoculated with PAS sensitive strains and animals inoculated with PAS resistant strains

Present Status of Chemotherapy of Tuberculosis with Conteben, a Substance of the Thiosemicarbazone Series is reviewed by Anton Mertens and Rolf Bunge[7] (Leverkusen Germany) Thus far over 10 000 patients with different forms and stages of tuberculosis have been treated with conteben (4-acetylaminobenzaldehyde thiosemicarbazone) and over 60 clinical reports have been written on experience in Germany Response of the infection to therapy is essentially a question of the respective reaction powers of tissue The more labile the disease and the better the blood supply the more promising conteben seems to be Extensive caseous processes respond less favorably to the medication Chronic pulmonary tuberculosis is least responsive The daily average dose of conteben is about one tenth by weight that required of streptomycin Drug resistant tubercle bacilli have not been detected thus far in treatment with conteben Everything seems to point to the fact that the thiosemicarbazones as well as streptomycin and para amino salicylic acid possess different modes of action on the tubercle bacillus The possibilities of an effective combination of these agents are obvious

Acute generalized miliary tuberculosis and tuberculous meningitis are not amenable to conteben therapy Tuberculous infections of mucous membranes such as the larynx tracheobronchial intestinal and bladder linings usually respond impressively Recently developed exudative type pulmonary tuberculosis often shows rapid recession under thiosemicarbazone therapy There is prompt improvement in the general condition and frequently an astonishing weight increase X rays show rapid recession of infiltration and the effect on temperature is evident

In general chronic hematogenous disseminated pulmonary tuberculosis responds quite well to conteben However in only a small number of the cases does the sputum become negative Impressive results have been reported with cavity

(7) Am Rev T bc 61 20 38 J ry 1950

was sensitive at 0 006 mg and CN844 to 0 025 mg/100 ml but these organisms isolated from three patients after 120 days therapy had a resistance 50 100 times greater

A blood PAS level similar to that produced clinically does not protect the tuberculous sensitized guinea pig from a lethal challenge dose of PPD OT nor does previous admixture and incubation modify the challenge

Experiments with skin temperatures in man show that PAS exerts a peripheral vasodilatation which increases heat loss by direct radiation and is observed in both febrile and afebrile tuberculous patients The increased heat loss in afebrile patients is compensated by an increase in the basal metabolic rate

The influence of PAS on prothrombin time and gamma globulin content of plasma are probably not significant

[Para aminosalicylic acid is of great interest now because of its usefulness in combination with streptomycin however used alone it seems to have a place in mild forms of tuberculosis particularly those which are more easily influenced such as early tuberculous bronchitis —Ed]

Increase in Resistance of Tubercle Bacilli to Sodium Para Aminosalicylic Acid Observations on Cultures Isolated from Patients during Chemotherapy Andre Delaude Alfred G Karlson David T Carr William H Feldman and Karl H Pfuetze[6] found cultures from 71 patients who had not been treated with para aminosalicylic acid (PAS) including 10 cultures which were resistant to streptomycin to be resistant to only 0 006 or 0 012 mg of sodium para aminosalicylic acid (NaPAS)/100 ml medium Eighteen of these patients were treated with PAS alone for 94 days or less At the end of therapy cultures from these patients were still resistant to 0 006-0 012 mg NaPAS/100 ml medium Four patients were treated with PAS promin* and streptomycin for 144-180 days Cultures of tubercle bacilli from these patients were likewise no more resistant to NaPAS than the cultures obtained before treatment Five patients were treated with PAS alone for 157 251 days at the end of which four discharged tubercle bacilli able to grow in the presence of 1 6 6 4 mg NaPAS/100 ml medium a concentration 200 500 times greater than that in which tubercle bacilli from untreated patients will grow

The significance of these findings will be known only after

(6) Proc Staff Meet. M yo Cl n 24 341 346 June 2 1949

more clinical experience with PAS which will make it possible to correlate occurrence of tubercle bacilli resistant to the drug in vitro with response to therapy An approach to this question may be made by comparing response to treatment with PAS of animals inoculated with PAS sensitive strains and animals inoculated with PAS resistant strains

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(7) Am R Tube 61 0 38 J u y 1950

drainage supplemented with instillation of 0 1 0 2 Gm of finely powdered conteben suspended in 1 2 cc pure glycerol In one series of cases complete bacteriologic disinfection of the cavities was obtained by this method Since pure glycerol increases the tendency to cough substitution of physiologic saline has proved advantageous In tuberculous empyema or pyopneumothorax local conteben therapy in the form of intrapleural instillation of a suspension of 0 1-0 5 Gm of the finely powdered drug in physiologic saline has been followed by favorable results Treatment is carried out three times a week and continued until exudate formation decreases

Conteben therapy should be instituted with the smallest possible doses e g 12 5 25 mg Depending on the patient s condition the dosage may be increased until there is subjec tive and objective improvement In general 200 mg a day is the upper limit of daily dosage Average daily dose is about 2 mg /kg body weight given orally

Secondary effects such as lack of appetite gastric com plaints or nausea and vomiting disappear in most patients despite continuance of medication Conjunctivitis exanthemas hemolytic anemia and agranulocytosis have been noted but usually in patients receiving large doses The likelihood of liver damage has not yet been ascertained

[The work with this substance in the United States has not pro gressed sufficiently to allow a definite evaluation Investigations in prog ress on other thiosemicarbazones may lead to finding one with less toxicity Although these substances are not as potent against tuberculosis as streptomycin they have considerable value when used in combination with or in successive cour es of various drugs —Ed]

Therapeutic Effect on Experimental Tuberculosis in Guinea Pigs of 4 Acetylaminobenzaldehyde Thiosemicarbi zone (TB1) Alone and in Combination with Streptomycin Alfred G Karlson J H Gainer and William H Feldman[7] inoculated 42 guinea pigs subcutaneously with 0 1 mg viru lent human tubercle bacilli (H37Rv) On the 29th day of in fection each animal had a subcutaneous abscess at the site of inoculation and enlarged regional lymph nodes On the next day the animals were divided into five groups and the follow ing treatment given (1) no treatment (2) 6 mg strepto mycin daily *(3) 0 1 per cent TB1 in the diet for 33 days* fol lowed by 0 2 per cent in the diet for 27 days (4) 2 mg strep

(7a) Proc. Staff Meet. M yo Clin 5 160-167 M 29 1950

tomycin daily (5) 2 mg streptomycin daily and TB1 in the diet as in group 3 Only three animals died After 60 days of treatment surviving animals were killed

The extent of tuberculosis seen at autopsy is shown in Figure 28 Animals treated with TB1 alone or in combination

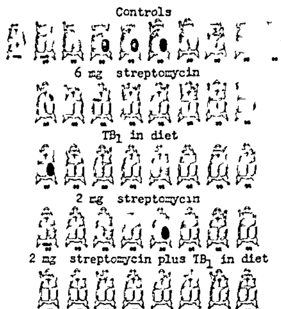


Fig 28.—Amount f t berculos seen t ecr psy n 42 gu nea p g inoculated w th t ber l bacill and treated ously The e pe ment nd days of treatment which tarted on the 30th day f i fect on N mer ls numbe f day of fect on the bla k ba mean that the nimal d ed be end f th experiment. Li er and pleen epresented by ecta gl espect ly The rrow nd cate th te f oculat on nd the black dot prese ts n bsc s ulcer espect ly The mall nd la g dots m liary d nodular lesions pect ly A mpletely bla kened org d ff se t be culous l ement. (Courtesy f Ka lson A. G et al P Meet., Mayo Cl n. 25 160-167 Mar 29 19 0)

with streptomycin had decidedly fewer grossly visible tuberculous lesions than the untreated controls Their lungs were entirely free of the necrotizing processes seen in untreated controls Grossly and microscopically there was evidence of more pronounced regression and healing of lesions than that achieved with 2 mg streptomycin alone but the beneficial effect was inferior to that which resulted with 6 mg streptomycin daily The combination of TB1 and streptomycin was only

slightly more beneficial than TB1 alone There was no micro scopic evidence in the lungs liver spleen or kidneys that TB1 was toxic

Action of Streptomycin and Usnic Acid on Development of Tuberculosis in Guinea Pigs is described by Alfred Marshak and Marvin Kuschner[8] After inoculation with 0 2 mg dry weight of H37Rv tubercle bacilli five groups of guinea pigs were established the first containing 19 and the others 20 animals each Group 1 was untreated usnic acid only was given to group 2 6 mg streptomycin daily to group 3 2 mg streptomycin daily to group 4 and usnic acid plus low doses of streptomycin to group 5 Group 5 received 20 mg usnic acid in oil tween* 80 mixture for 6 days 10 mg daily for 24 days and 2 mg streptomycin daily for 30 days In all treated groups administration was started on the day after inoculation and maintained for 30 days All surviving animals were killed 41-44 days after inoculation

There were five deaths in the entire series of 99 animals all in group 5 However none were due to tuberculosis The rates of weight gain and the final total gain in groups 1 3 and 4 were fairly comparable but in groups 2 and 5 which received usnic acid there was little gain until after cessation of therapy In groups 3 and 5 85 94 per cent of the animals had either no evidence of disease in the liver or the mildest form This was in striking contrast to the other groups in which only 10 40 per cent of the animals had slight changes Evaluation of gross lesions in the spleen gave a similar distribution Microscopic examination of spleen and liver lesions showed results similar to those obtained by gross inspection In general distribution of lesions in the lungs was similar to that in the liver and spleen

A comparable marked retardation of disease was obtained with high doses of streptomycin or with usnic acid combined with low doses of streptomycin There was no evidence that usnic acid alone in the doses given affected the severity of the disease to any degree The definite effect achieved in group 5 indicates a clear potentiating action of usnic acid on streptomycin since small doses of streptomycin alone caused little retardation of disease Both streptomycin and usnic acid may affect the desoxyribonucleic acid desoxyribonuclease

(8) P b H lth R p 65 131 144 F b 3 1950

cellular system but in different ways one acting on the substrate the other on the enzyme This observation may account for the synergistic action of the two substances Although streptomycin alone in sufficiently large doses is more efficient than usnic acid the synergistic action of the two drugs may limit development of resistance

Use of Antihistaminic Drugs in Human Tuberculosis Although primary tuberculosis is usually relatively benign this characteristic is reversed in the reinfection or secondary phase This reversal depends on hypersensitivity to an antigen which is developed during the primary phase and maintained as long as tubercle bacilli remain within the body On reinfection or spread of the bacilli from a primary site an inflammatory reaction occurs which is characterized by exudation and may be followed by caseation necrosis If this acute inflammation could be prevented a significant advance in tuberculosis therapy would be achieved It seemed possible to A R Judd and Alfred R Henderson[9] (Hamburg Pa) that antihistaminic drugs might protect sensitized cells from injury and thus alter the course of the disease

Thirty patients with pulmonary and nonpulmonary tuberculosis were given various antihistaminic drugs in doses starting at 50 mg three times daily and increasing to 300-400 mg daily as tolerated Clinical response was graded roentgenographically and by temperature changes character and quantity of sputum and increase in weight appetite and feeling of well being The greatest improvement occurred in patients with tuberculous pneumonia and other acute exudative lesions which the authors believe are a result of hypersensitivity As the lesions progressed in chronicity the antihistaminic drugs became less effective

Positivity of Mantoux tests diminished gradually in most instances as therapy was continued The reaction returned to its former level within four to six weeks after administration of the antihistaminic was stopped Although skin sensitivity is not necessarily a measure of hypersensitivity in other tissues it would appear from these results that clinical improvement roughly parallels suppression of the Mantoux reaction

Three patients who showed striking improvement with antihistaminic therapy were taken off this medication Within

(9) A n All gy 7 306 317 M y J 19 9

two to eight weeks symptoms and signs of the disease re curred and retrogression of pulmonary lesions was demon strable by x rays Reinstitution of therapy was again followed by striking improvement in all three patients

[Experience thus far does not lend support to the concept that anti histaminic drugs will be helpful in treating the so called allergic mani festations of tuberculosis The presence of active infection is the central factor responsible for clinical symptoms and other phenomena, and treat ment must be aimed fundamentally to control this infection The view that the difference between primary tuberculosis and so called reinfec tion disease is related principally to tissue hypersensitivity is too narrow to explain all the observed features of the disease In this connection it is of interest that Abelson (Lancet 1 1018 May 27 1950) reports no effect from antihistaminic drugs on the intensity of the tuberculin skin reaction —Ed]

Resected Post thoracoplasty Lung William A Meissner Richard H Overholt Norman J Wilson and James H Walker[1] (Boston) studied 62 instances of thoracoplasty failure in which pulmonary resection was performed One factor that hampered adequate analysis of the material was the difficulty in distinguishing pathologically between cause and effect of thoracoplasty failure Cause can best be determined when the clinical findings are correlated with the pathologic picture

The outstanding contributory cause of failure was a tech nically inadequate thoracoplasty Adequate collapse of the cavity bearing area was obtained in only 14 instances Col lapse was totally inadequate in 40 The factors causing this failure were (1) transverse processes not resected (2) long anterior stumps (3) inadequate number of ribs resected (4) delayed stages and (5) failure of rib regeneration

Another important contributory cause was poor case se lection The patients were predominantly middle aged with long term illnesses Only 18 had had no prethoracoplasty col lapse therapy The facts indicate that this group of patients was brought to pulmonary resection late and at a time when many of them were poor risks

A third notable cause contributory to failure of thoraco plasty was a consequence of individual characteristics of the disease process the most important of which was the presence of large and giant cavities An unfavorable position of the cavity in the lower lobe was another characteristic of appar ent importance Endobronchial tuberculosis particularly when stenotic or bronchiectatic as well as exudative disease were

(1) Am. Re Tuberc 60 406-418 Oct ber 1949

likewise individual features of the disease process which seemed to inhibit good results from thoracoplasty

The fourth group of factors of importance were those of a mechanical nature which prevented adequate collapse and compression Such features as thickened cavity wall thick pleura and fibrotic indurated lung are examples of this group

[This analysis of the rea ons for failure of thoracoplasty should be a useful guide in helping to determine the strict indications for the opera tion the desirab lity of adequate collap e and the probable ineffectiveness of thoracoplasty in many cases in which it would be better to consider some other procedure such as lobectomy or another form of resection —Ed]

CHRONIC PNEUMONIA LUNG ABSCESS

Chronic Pneumonitis Its Clinical and Pathologic Im portance, Report of 10 Cases Showing Interstitial Pneumo nitis and Unusual Cholesterol Deposits William R Waddell Ronald C Sniffen and Richard H Sweet (Massachusetts Gen l Hosp) studied 10 patients treated by surgical resection of the diseased lobe or lobes The disease was initiated by an acute respiratory infection in five and in five onset was in sidious During the course of the infection there were exacer bations and remissions of acute episodes The principal chronic symptoms were fever cough expectoration and occasional hemoptysis pleuritic pain and weight loss Duration of symp toms varied from nine weeks to five years but 9 of the 10 patients had been ill one year or less

Physical findings were usually those of consolidation of a portion of the lung but sometimes signs were absent On roentgen examination a variable portion of the lung usually showed evidence of atelectasis or consolidation and although the appearance sometimes suggested that of an inflammatory process the possibility of carcinoma could seldom be ex cluded with certainty (Figs 29 and 30) Bronchoscopic ex amination usually showed no abnormality and bronchograms were not helpful

In 6 of the 10 cases carcinoma of the lung was diagnosed preoperatively but at operation it was possible to recognize

(2) J Th S g 18 707 737 O t b 1949

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(2) J Thor S g 18 707 737 O tobe 1949

the inflammatory character of the disease The technical diffi culties in resection cannot be overemphasized In addition to inflammatory reaction about the hilus in some cases pleural adhesions were so dense and vascular as to constitute a major technical difficulty Patients observed early in the series were given sulfadiazine both pre and postoperatively and those observed later received penicillin There were no postopera tive complications and all patients were relieved of symptoms and returned quickly to health

The principal importance of chronic pneumonitis of the



F g 29 —Post te film F g 30 —S me c L ft l t l film (Co t y f W dd ll W R J Tho ac S g 18 707 37 O t be 1949)

type seen in these 10 patients is that it may be confused with carcinoma of the lung If progress is to be made in manage ment of carcinoma of the lung exploratory thoracotomy must be used more often in doubtful cases However at exploration differentiation between neoplastic and chronic inflammatory disease may be difficult Under such circumstances examina tion of a frozen section may be necessary If such examina tion rules out carcinoma it is possible to limit operative pro cedure to lobectomy instead of pneumonectomy It is obvious however that a negative biopsy does not exclude carcinoma for an inflammatory process similar to this may occur distal to a malignant lesion when there is bronchial obstruction

The gross and microscopic changes found in the lungs of the various patients were essentially similar but in different

stages in evolution of the process Degree of involvement could not be anticipated from the apparent duration of the disease The affected lobe was always decreased in volume and fibrous adhesions of varying density were scattered over



F g 31—S m p d g L b h b en ect d d l d p t dem t t l t t g f h p mo t h t d by fib d p t hy mphy m (Cou t y f W ddell W R t l J Th c S g 18 707 737 O tobe 1949)

the pleural surfaces The bronchial lymph nodes were en larged and firm Section showed that the pneumonic process had usually involved the entire lobe or the major portion of it In the comparatively early stages of the process the most arresting aspect of the cut surface was the intense yellow color of the diseased parenchyma In more advanced stages

the gross appearance was that of increasing fibrosis The intense yellow color had faded and was replaced by gray fibrous tissue lightly flecked with golden yellow dots that were sometimes segregated in areas of varying size throughout the lobe Localized areas of emphysema were sometimes present in the fibrosed parenchyma (Fig 31) No obstructing lesion was found in the large bronchi

Microscopic examination of the 10 lobes showed chronic pneumonitis in which the end result was extensive fibrosis of the involved segments The earliest changes detected consisted of flooding of the primary lobules by a great number of large mononuclear cells Many cells were vacuolated their microscopic appearance being similar to xanthoma cells The substances within the monocytes were strongly sudanophilic and doubly refractile and were believed to be largely cholesterol and cholesterol esters The Schultz reaction for cholesterol and cholesterol esters was strongly positive Chemical analysis of tissue taken from grossly yellow areas of lung gave extremely high values for cholesterol and cholesterol esters

[The pathogenesis of this condition is not clear As the authors suggest it is possible that the cholesterol deposit is a feature of chronic inflammation. This is observed in chronic inflammations in other sites such as long standing chronic empyema —Ed]

Correlation between Roentgenologic and Pathologic Findings in Chronic Pneumonitis of Cholesterol Type The process described by Laurence L Robbins and Ronald C Sniffen[3] (Massachusetts Gen l Hosp) is characterized by its chronicity with either acute or insidious onset but has not been previously recognized in the absence of bronchial obstruction or significant coexistent lung disease Of 11 patients all but 1 were males Ages ranged from 12 to 67 X rays showed that the process involved a lobe extensively in five patients whereas in the others the lesion was localized to a portion of one or more segments Pleural thickening pleural fluid mediastinum or hilar lymph node enlargement or rarely small cavities were observed

Since none of the specimens were available for examination less than 1½ months after onset the earliest phases of the inflammatory process were not encountered The affected lobe was always contracted in rough proportion to the amount

(3) Radiology 53 187 0 August 1949

of fibrosis Bronchial lymph nodes often reached a diameter of 2 cm The diseased tissue fanned out from the hilus to assume a pyramidal shape with the base at the pleura In its comparatively early phases the involved lung tissue was an intense yellow but as healing progressed the parenchyma became gray and fibrous The larger bronchi of the diseased lobes were chronically inflamed and thickened and the smaller bronchi were occasionally acutely inflamed dilated and obviously destroyed with their lumens filled by tenacious mucopurulent material

Microscopically the earliest alteration encountered in the parenchyma was massive influx of large mononuclear cells with central or eccentric nuclei and voluminous cytoplasm composed of a foam of fine droplets This was accompanied or followed closely by a chronic interstitial pneumonitis beginning in the connective tissue septa from which lymphocytes plasma cells and edema spread to peribronchial and perivascular regions and the alveolar walls In addition alveolar septal cells became intensely swollen Next vacuolated macrophages gradually accumulated within the alveolar walls resulting in obliteration of the alveolar spaces because of marked swelling of the walls A foreign substance in the form of fine intracytoplasmic vacuoles lay within the large monocytes of the air spaces and alveolar walls Various tests suggested that this was cholesterol The end results of the process are unknown since only operative specimens were studied but the evidence at hand favors fibrosis as the final stage Origin of the cholesterol is unknown but there is no evidence that it is produced locally In general the changes are those of tissues dealing with a foreign substance though hampered in their efforts by mild secondary infection

Major Etiologic Factors Producing Delayed Resolution in Pneumonia Theodore K Gleichman Max M Leder and Daniel W Zahn[4] (Veterans Admin Hosp Fort Logan Colo) investigated the cause of delayed resolution in 52 cases In 50 the chief etiologic factors were determined but in 2 no clear underlying cause could be demonstrated The major process responsible for delayed resolution was impaired bronchial drainage in 22 cases (42 3 per cent) in 4 of which the cause proved to be bronchogenic carcinoma These lesions

(4) Am J M S 218 369 373 Oct 1949

early diagnosis and definitive treatment of which was delayed for some months by treatment for pneumonia proved to be nonresectable

A specific organism or chemical insult was responsible for delayed resolution in 16 cases (30 7 per cent) Aspiration was the commonest cause in this group and in five of the six patients single or multiple lung abscesses developed Fried lander s pneumonia occurred in four patients all of whom recovered under streptomycin therapy Intrinsic complications of the pneumonic process caused delayed resolution in 12 cases (23 per cent) Most of the patients were in the younger age group and had extensive lesions treatment of which was instituted late or in which bacteriologic study was inadequate Four of these patients had lung abscess four lobar or seg mental collapse two pleural effusion and two empyema

[One should never be content with the diagnosis of delayed resolution of pneumonia without ascertaining the cause which often may be reme died—Ed]

Studies in Lung Abscess Treatment. Although lung ab scess includes a variety of conditions which require different methods of treatment R C Brock[5] states that certain general principles apply to all lung abscesses Fundamentally treat ment does not differ from that needed for a suppurative proc ess elsewhere in the body In deciding whether surgery is necessary a balance must be struck between the risk of fur ther delay and the risk of the operation itself A radical opera tion such as lobectomy or pneumonectomy may be better than simple external drainage

Lung abscesses are always hazardous The teaching that if let alone the abscess will probably heal by itself is danger ous and cannot be upheld by a critical study of results Lung abscess and lung suppuration should be considered essentially surgical conditions but expectant management such as bed rest provision of adequate fluids calories protein and vita mins correction of anemia and use of appropriate chemother apy are also important

Chemotherapy has cured many lung abscesses but if con tinued when drainage of pus is needed may be harmful In correct or inadequate administration of chemotherapeutic agents is also to be avoided If possible the etiologic agent

(5) Guy Hosp R p 97 196 229 1948

should be identified so that the sulfonamide or antibiotic to which it is most sensitive can be used Early and vigorous *treatment is likely to be successful* but if slough is present rapid and complete dissolution is unlikely without operation Penicillin can be used topically as well as parenterally

The chief physical method useful in expectant management *is postural drainage* In abscess of the axillary areas the patient should lie on his side for abscess of the apical segments of the lower lobe the patient should be prone for abscess of the middle lobe he should be placed on his back with the foot of the bed slightly raised The proper position for postural drainage can be prescribed only after careful study by lateral and posteroanterior x rays of the segment or segments involved and the direction of the draining bronchus Should the patient cough up more sputum in some posture other than the one which appears to be most favorable that position is to be encouraged Postural drainage should be carried out for as many hours of the day as the patient can tolerate it It may be supplemented by vibration or hacking and clapping applied intelligently and not too severely Combined with chemotherapy these measures are often helpful

The chief value of bronchoscopy lies in investigation and diagnosis rather than in treatment In general every patient with a lung abscess should have bronchoscopy but under certain circumstances it is unnecessary Striking improvement from bronchoscopic treatment is too infrequent or unconvincing to lead to its wide or confident adoption Its actual therapeutic value is due as much to stimulation of coughing as to aspiration of pus except in rare cases usually in the lower or middle lobes when the sucker can be manipulated into the abscess

Poor *postoperative results are due not to surgery but to* delayed surgery If operation is undertaken at the right time only minimal permanent damage if any should remain It is a fallacy that operation should not be contemplated until the abscess has been allowed at least six weeks to heal under expectant management After six weeks an acute lung abscess has become chronic and is not susceptible to simple external drainage As soon as the physician is satisfied that an acute lung abscess fetid or nonfetid is not making satisfactory and uninterrupted progress toward recovery it should be drained

immediately Unless the systemic reaction cough with sputum and x ray changes have shown consistent improvement or are no longer present surgical intervention is necessary

External drainage of a lung abscess may be an easy and satisfactory operation if properly planned The essential preliminary is to localize exactly the particular segment of lung involved and assess the area of presentation If the anatomic localization is correct a one stage operation is almost always possible for the pleura is adherent over all the abscess except when the chief presentation is interlobar mediastinal or diaphragmatic In such cases a two stage operation may be unavoidable The general principles outlined in expectant management including intramuscular use of penicillin should be continued postoperatively The pack placed in the cavity at operation should be replaced by a properly selected tube after 14-20 days The ever present danger of secondary hemorrhage constitutes one of the greatest operative risks If bleeding occurs the wound should be inspected in the operating room Pleural effusion may occur even if there was no obvious opening of the pleura It may be controlled by aspiration and injection of penicillin but if empyema develops drainage is required The other postoperative dangers are spread of the pneumonic process with fresh lung abscesses and development of cerebral abscess

Among 280 patients treated by expectant management only 40 per cent were cured 7 5 per cent died and 52 5 per cent experienced nonresolution Among 188 treated by surgical means (these included patients who did not respond to expectant management) 25 1 per cent died 63 6 per cent recovered and in 11 3 per cent chronic processes developed With a view to improving the results of external drainage lobectomy or pneumonectomy was used in 50 cases Three deaths followed lobectomy and four pneumonectomy but since the old tourniquet technic of operation has been abandoned there has been only one death in the last 22 lobectomies and one in the last 10 pneumonectomies Results in all but one of the patients who recovered were satisfactory and in most were excellent The best hope of securing a good result with greater safety lies in wider use of lobectomy or pneumonectomy Such treatment should be instituted in an earlier phase in treatment than has been customary The important decision is

not whether lung abscess should be treated by medical or surgical means but which patient will do well without operation and in which operation is indicated

[The availability of antibiotic drugs has greatly influenced the treatment of lung abscess external drainage is not practiced nearly as much as it was 10 years ago Resection of the diseased lobes or segments of lobes is carried out more frequently to remove destroyed and damaged tissue which might otherwise be the seat of chronic and repeated infections —Ed.]

Treatment of Lung Abscess Experience with 32 consecutive cases of acute lung abscess led A W Sutherland and L J Grant (London Chest Hosp) to conclude that penicillin and postural drainage can completely cure lung abscesses and provide results superior to those of other methods

The optimal dosage of penicillin is 2 000 000 units of the calcium salt daily given in four intramuscular injections This dosage is maintained three to four weeks After the pulmonary segment involved is determined the best anatomic position for postural drainage is ascertained and treatment given under the supervision of an experienced physical therapist Controlled coughing is required to assist drainage In the early days of treatment many hours should be spent in the correct posture for maximal drainage as sputum diminishes six periods of ½ ¾ hour may suffice gradually decreasing until the cavity is obliterated

Of 19 patients treated by this method 15 were cured A diabetic patient who was semicomatose when admitted died Chronic bronchiectasis developed in two and the third has x ray evidence of residual localized bronchiectasis Only three of six patients were cured by treatment with half as much penicillin Of seven patients treated by surgical drainage only three were cured drainage continued for an average of 28 weeks before healing Two patients in the first group in whom chronic abscesses developed were treated by surgical resection and within four weeks were cured and ready for work

[In most clinics abandonment of external drainage of lung abscesses with few exceptions is one of the vast improvements wrought by the antibiotics This article probably refers chiefly to putrid abscess Most nonputrid abscesses are due to gram positive cocci and have an even better prognosis However those due to Friedlander bacillus do not respond to penicillin

In all cases after clinical recovery a determination of the extent of the residual abscess if any should be made Bronchograms may be needed for this purpose —Ed]

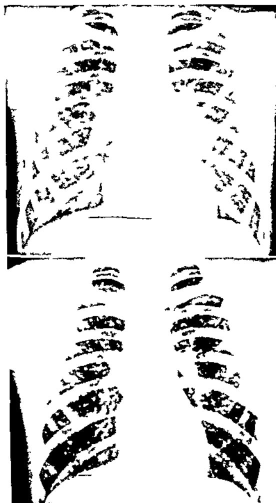
(5) Lancet 1 530 532 Mar 25 1950

MYCOSES

Development of Calcification in Pulmonary Lesions Associated with Sensitivity to Histoplasmin As a result of intensive studies during the past few years evidence has accumulated which suggests that histoplasmosis—formerly believed to be a rare and usually fatal disease—may exist as a mild asymptomatic syndrome which is very prevalent in certain parts of the world The principal significance of the asymptomatic form is that in certain respects the disease so closely resembles tuberculosis as to be frequently confused with it The most striking similarity between the two diseases lies in the fact that in both there are pulmonary calcifications which are so alike in appearance as to be indistinguishable except that some occur in people hypersensitive to tuberculin and others in people hypersensitive to histoplasmin In tuberculosis it has been well established that the antecedent lesion is a soft type of infiltrate in a tuberculin positive individual from whom it is often possible to recover tubercle bacilli Rather similar soft lesions have been found in histoplasmin positive tuberculin negative persons and the fungus Histoplasma capsulatum has been recovered in some Although this type of evidence leaves little doubt that healing by calcification does take place in histoplasmosis as it does in tuberculosis demonstration of calcification developing in pulmonary infiltrates in histoplasmin positive persons has not yet been presented convincingly

By periodic routine school x ray and skin testing surveys in Kansas City Michael L Furcolow[6] (U S Pub Health Service) found several hundred histoplasmin positive tuberculin negative children with pulmonary infiltrates These children have been followed for periods up to four years during which time some of the infiltrates disappeared some apparently became fibrotic but most gradually became calcified In the entire group no new lesions appeared nor was there progression of the initial lesion The author presents case summaries and films of each of 17 children most of whom had lived all their lives in or near Kansas City All were com

(6) P b Health R p 64 1363 1393 N 4 1949



F g 3 (t p) —Ch t film f b y 13 t ken 4/10/45 M l y l ns g d h t pl m
F g 33 (b tt m —S me 6/22/49 C lt f g t t t y ld d H t pl m p l t m Of ght compl m t fi t n t t f h t pl m w p t th p d th g t
(C t y f F l w M L P b H lth R p 64 1363 1393 N 4 1949)

pletely asymptomatic at the time of the survey and throughout the observation period with no history of any type of illness which could be related to development of the infiltrate

In general the precalcific lesions may be classified as disseminated infiltrates pneumonic infiltrations or nodular foci The disseminated infiltrates consisted of multiple lesions scattered throughout both lung fields The individual infiltrates were uniformly millet seed in size in some whereas in others they ranged from a few millimeters in diameter to large conglomerate patchy areas (Fig 32) Calcifications resulting from disseminated infiltrates were distributed throughout the parenchyma (Fig 33) with variation in size and shape corresponding to the distribution and extent of the infiltrates In the miliary type the calcifications were small fairly round and equally distributed throughout the lung fields presenting a picture once thought to represent healed miliary tuberculosis

Pneumonic infiltration usually consisted of a small area of infiltration poorly circumscribed and irregular in shape although in one case there was a rather diffuse type of pneumonitis Calcification appeared in scattered small foci throughout the lesion or as a single lesion in the mid t of a clearing area Nodular lesions consisted of well defined nodular shadows ranging in size from 0 5 to 4 cm in diameter A calcified central core developing in the nodule was characteristic although in many cases the calcification appeared to replace the entire lesion or developed in multiple small areas within the infiltrate

[The members of the U S Public Health Service have done a remarkably useful task in separating and helping to identify the pulmonary calcifications of apparently nontuberculous origin Diagnostically it is a useful distinction in some cases to note that these calcifications seem to be distributed a little more heavily toward the bases of the lungs and that the individual shadows have a very homogeneous smooth texture In contrast tuberculous calcifications more often predominate in the upper parts of the lungs are likely to be more irregular in size and more granular in texture—Ed]

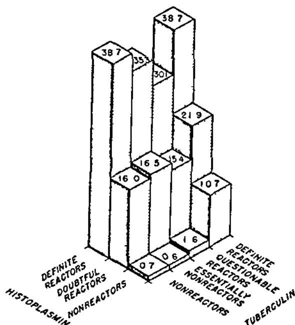
Studies of Pulmonary Findings and Antigen Sensitivity among Student Nurses—*Relationship of Pulmonary Calcification with Sensitivity to Tuberculin and to Histoplasmin*—Jennie C Goddard Lydia B Edwards and Carroll E Palmer[7] (U S Pub Health Service) observed the incidence of tuberculin and histoplasmin sensitivity and pulmonary calcification

(7) P b. He lth Rep 64 820 846 J ly 1 1949

in 16 320 student nurses in 76 nursing schools in 10 metropolitan areas in the United States Positive tuberculin reactions were those with induration 5 mm or more in diameter which appeared following 0 0001 mg PPD (Seibert) Induration of any size or erythema of 5 mm or more in diameter following intradermal injection of 0 1 cc of a 1 1 000 dilution of histoplasmin a filtrate of broth culture of Histoplasma capsulatum was a definite reaction Pulmonary calcification was evaluated by means of x rays Some reaction to histoplasmin occurred in 19 5 per cent and some reaction to tuberculin in 15 5 per cent Histoplasmin sensitivity ranged from the high rate of 65 per cent in Kansas City Mo to the relatively low rate of 7 per cent in Minneapolis The high rate for tuberculin reactors was 22 8 per cent in Philadelphia and the low 7 9 per cent in Minneapolis The highest incidence of pulmonary calcification 27 3 per cent was found in Kansas City Mo and the lowest 2 6 per cent in Minneapolis Areas having high rates of frequency of pulmonary calcification corresponded to those having high rates of sensitivity to histoplasmin and vice versa

Figure 34 shows in three dimensional graphic form the calcification rates for the 12 subgroups The column labeled 10 7 indicates that 10 7 per cent of nurses who are definite tuberculin reactors and histoplasmin nonreactors show pulmonary calcification in the chest films The other bars indicate the relative frequency of calcification in the various other subgroups Considering the front row of columns to the right which gives calcification rates for different categories of tuberculin reactors among histoplasmin nonreactors it is apparent that very low rates prevail except for the definite tuberculin reactors The difference in the frequency of calcification in those who were questionable reactors and who therefore were given 0 005 mg of PPD S and those who were definite tuberculin reactors indicates that for practical tuberculosis work little is to be gained by testing with large doses of tuberculin Further examination of Figure 34 discloses that for purposes of selecting cases showing that type of calcification associated with sensitivity to histoplasmin the point of separation between specific and nonspecific histoplasmin reactions is most efficiently made by designating the nonreactors negative and both definite and doubtful reactors positive

Study of the back row of bars shows that the frequency of calcification in nurses who are definite reactors to both antigens is less than theoretically would be expected and that nonreactors and definite reactors to tuberculin have the same frequency of calcification while those with intermediate levels of tuberculin sensitivity have lower rates of calcification Ap



F g 34 —Percentage of t dent n rses w th pulmo ary calc fic t n d g to h toplasm n a d to tube cul n e ctı s (Courtesy f Godda d J C t al P b Health R p 64 8 0 846 J ly 1 1949)

parently some undetermined factor exists which affects the association between reactions to tuberculin and histoplasmin and the development of pulmonary calcification

The basic relation between pulmonary calcification and sensitivity to histoplasmin and tuberculin remained essentially unchanged between the different geographic areas of the study About one third of the nurses reacting to one or both antigens had pulmonary calcifications about one tenth of those reacting only to tuberculin had calcification and only 0 7 per cent with a reaction to neither had calcification From

Figure 34 it is apparent that calcification among reactors to histoplasmin alone was three times as high as among reactors to tuberculin alone This together with the higher average prevalence of histoplasmin as compared with tuberculin re actors indicates that much more calcification was associated with histoplasmin than with tuberculin sensitivity On the other hand the rarity of calcification in those who reacted to neither antigen indicates that tuberculosis and whatever causes sensitivity to histoplasmin account for almost all the calcification observed

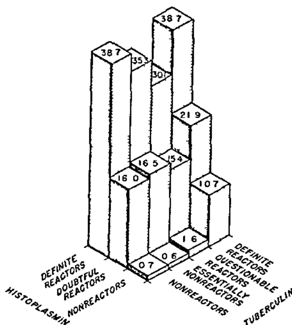
[This statistical analysis seems to focus considerably on the likely causes of pulmonary calcifications Since histoplasmin is not a wholly specific antigen further work is required to demonstrate whether one or more infections may be responsible for calcifications unrelated to tubercu losis —Ed]

Doubtful Reactions to Tuberculin and to Histoplasmin — Carroll E Palmer and O Strange Petersen[8] analyzed results of tuberculin and histoplasmin tests and x ray examinations in over 16 000 nurses from the 10 widely separated metropoli tan areas in the United States Reactions to most tests form a continuous scale from large apparently typical responses to no observable reaction The existence of nonspecific re actions creates special problems in interpretation Since posi tive and negative reactions are distributed over the scale it is supposed that positive reactions tend to be at one end and negative reactions at the other with some overlapping in a zone on the reaction scale Reactions in this intermediate zone may be designated as doubtful or questionable and be cause it is not possible to distinguish them individually the group consists of a mixture of erroneously classified true positive and true negative reactions This hypothesis of erro neous classifications offers a plausible and extremely simple explanation of findings which would not be easy to interpret otherwise

In cities which had the highest prevalence of histoplasmin reactors (Kansas City Mo and Columbus O) and in which a high proportion of doubtful groups may be regarded according to the theory as true positive reactors little dif ference was found in the frequency of pulmonary calcification for the definite and doubtful reactors to histoplasmin In cities with a low prevalence of histoplasmin reactors (San

(8) P b H lth R p 65 1 32 J 6 1950

Study of the back row of bars shows that the frequency of calcification in nurses who are definite reactors to both antigens is less than theoretically would be expected and that nonreactors and definite reactors to tuberculin have the same frequency of calcification while those with intermediate levels of tuberculin sensitivity have lower rates of calcification Ap-



F g 34—P ntage of tudent n ses w th p lm n ry calcificat cco d g t h toplasmin and to tub ul n ti n (C rt y f Godda d J C *et al* P b Health R p 64 820 846 J ly 1 1949)

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Family Endemic of Geotrichosis Pulmonum is reported by Th Thjotta and Knut Urdal[9] (Oslo Univ) Chest x rays of two patients showed changes suggestive of tuberculosis One of these patients also had a diseased hip joint thought to be tuberculous Since both patients were tuberculin negative and Mycobacterium tuberculosis had never been found in the discharges further bacteriologic examination of the sputum was made and a typical strain of geotrichum (species unknown) was disclosed Sputum specimens from the whole family of eight persons were examined Geotrichum was found in three making a total of five members of the same family with infection due to this organism All the patients had negative tuberculin reactions and Myco tuberculosis was never found in the sputum

The sputum contained mycelial threads and chlamydospores or arthrospores of the fungus On Sabouraud's agar the colonies grew as fairly large adherent membranous plaques with a white or grayish surface Morphologic biochemical and serologic tests indicated that the fungus was geotrichum It was not pathogenic for rabbits and guinea pigs

The patients probably were infected from soil dust containing spores since all lived on or near the same farm Since one of the patients had been sent to a sanatorium for treatment of tuberculosis it is emphasized that lung mycoses may simulate tuberculosis

[Protracted and atypical pneumonia particularly of a bilateral diffuse distribution often raises the question of fungous infection but this is seldom the cause Usually some other etiology especially tuberculosis is demonstrated. Well authenticated cases of bronchopulmonary mycosis are therefore always of interest The infection usually appears to be inhaled and a careful history may elicit at least a strong suspicion of the source usually in the soil or some organic material The preceding and following reports are highly suggestive of such sources The recent report of C W Emmons (Am J Pub Health 40 436-440 April 1950) is relevant with respect to histoplasmosis He has found reservoirs of this infection in soil and in various animals around farms in southeastern parts of the United State The dog mouse rat cat, skunk and opossum have been identified as possible hosts of the infection —Ed]

Bronchopulmonary Mycosis Simultaneous Primary Occurrence in Four Children and Their Mother with Subsequent Healing by Diffuse Miliary Calcification 12 Year Observation is reported by Brenton M Hamil[1] (Henry Ford Hosp) Dur

(9) Acta [illegible] th [illegible] t m crob 1 Sc [illegible] d 26 73 681 1949
(1) Am J D[illegible] Ch ld 79 233 71 F bru[illegible] y 1950

Francisco Denver and Minneapolis) the frequency of calcification was much lower among the doubtful reactors tending to approach the low rate found among the nonreactors Analysis of the data showed that the frequency of doubtful reactors among nurses in the different cities was approximately what it would be if a certain percentage of true positive and true negative reactors had been misclassified as doubtful reactors This analysis furnishes further support for the hypothesis of erroneous classification

In contrast to the findings for histoplasmin the frequency of questionable reactors to tuberculin did not appear to be correlated with the prevalence of reactors but seemed to fluctuate around 5 per cent However the hypothesis would suggest that a little less than 5 per cent of the true positive and of the true negative reactors had been classified as doubtful The data indicate that the proportion of true positive reactors included in the questionable group varies with the level of sensitivity providing further support for the hypothesis In testing the hypothesis in terms of the frequency of pulmonary calcification in questionable tuberculin reactors calcification was expected in 2 3 per cent of the total group The actually observed frequency was 1 8 per cent

To account for the existence of nonspecific reactions the hypothesis was extended to include a third distribution superimposed on that of positive and negative reactions Examination of the data showed that application of this concept resulted in distortion of observed distributions of tuberculin reactions Further analysis suggested that in the prevalence of nonspecific reactions there is a geographic pattern quite different from the pattern of specific reactions

Certain tuberculin reactions particularly those resulting from the high doses currently in use are actually nonspecific They probably arise as cross reactions from tuberculin hypersensitivity produced by infection with other alcohol acid fast organisms

[It is well known that saprophytic mycobacteria may produce mild hypersensitivity and that these organisms frequently gain access to the body usually being ingested with vegetable foods Whether they actually set up lesions which give rise to confusing cross reactions with tuberculin remains to be proved but the hypothesis warrants further investigation —Ed]

Treatment included general supportive and symptomatic measures. After a diagnosis of bronchopulmonary mycosis, intensive treatment with iodides was instituted. Potassium iodide as much as 120 gr three times daily was given simultaneously with daily intravenous injections of 10 Gm sodium iodide in 100 cc water up to 30 days. Oxophenarsine hydrochloride was administered intravenously to some patients; later in the study inhalation of ethyl iodide was used. During the fourth week of treatment with the latter agent one patient developed transverse myelitis and at this time one specimen of spinal fluid yielded M pinoyi. Autogenous vaccines were prepared for two patients and a course of desensitization was carried out. The vaccine for one was made from cultures of aspergillus from the bronchus and for the other from cultures of M pinoyi. Adequate administration of iodide was considered the measure of greatest value in arresting disease in these patients.

X-ray findings at present indicate complete healing of the pulmonary lesions consistent with the good health of all the patients.

Acute Pulmonary Aspergillosis. A J Hertzog, T S Smith and M Goblin[2] (Minneapolis) report two cases with rapidly fatal course occurring in siblings.

Boy 5 had been in good health until one month before hospitalization when symptoms of an acute respiratory infection developed. On admission he had fever, respiratory rate was 84 and he was cyanotic. Chest films revealed diffuse bilateral pulmonary infiltration (Fig 35), thought to be consistent with pulmonary tuberculosis. Cultures from the throat and cultures of blood, spinal fluid and aspirated lung material showed no growth of fungi or bacteria. Therapy with penicillin, streptomycin and sulfadiazine resulted in no improvement and the child died 20 hours after hospital admission.

Autopsy revealed small flat grayish white areas studding the lung surfaces. Both lungs showed generalized consolidation with marked decrease in crepitation. Section revealed discrete and confluent grayish white nodules scattered diffusely throughout all lobes. Such nodules were not found on gross examination of the other organs.

Microscopic examination of the lungs demonstrated a widespread patchy granulomatous inflammatory process with tubercles composed of a center of neutrophils and a peripheral zone of epithelioid and large multinucleated giant cells (Fig 36). Granulomas

(2) P d t s 4 331 336 S pt mb 1949

ing the fall preceding illness all the patients had used old fashioned flails to pound wheat out of unthreshed stalks and had inhaled a great amount of moldy dust while harvesting grain and hay Cultures were not obtained from these sources but cultures from well water and feather beds yielded Aspergillus niger Aspergillus fumigatus two other strains of aspergillus and mucor penicillium and alternaria The patients tissues may have become sensitized to the protein of the organisms or an acute episode of influenza in all may have produced changes in the respiratory tract which favored continuous growth of the organisms The patients maintained contact with the various fungi during illness by continued use of the feather beds About two weeks after recovery from influenza exacerbation occurred with rising pulse weakness profuse sweating and persistent and distressing cough After these episodes of acute illness the patients appeared well About a year later symptoms developed similar to those of the exacerbation No physical signs were noted

During the observation period before treatment or laboratory studies other than x ray examination had been carried out the mother was killed in an accident Sputum stomach washings and stools of all the children were negative for tubercle bacilli Inoculations of guinea pigs with concentrated sputums and stomach washings of each child gave negative results for tuberculosis One guinea pig showed aspergillus in cultures from the spleen and another penicillium in the spleen and mucor in the liver The yeast organism most commonly found in the sputum of all patients was Monilia pinoyi This organism and mucor were grown from cultures of bronchoscopic smears of silver white plaquelike lesions on the bronchial mucosa of two patients The sedimentation rate was valuable for indicating activity or arrest of tissue destruction The white blood cell and differential counts were similar to those in tuberculous infection at comparable stages Repeated tests with all tuberculin materials used were negative up to a concentration of 1 mg /test dose

The x ray picture of the lungs was that of hematogenous tuberculosis In the early stage there were soft fluffy parenchymatous lesions which became condensed through fibrosis Deposition of calcium appeared on a few then all of the nodules as healing progressed

The finding of pathogenic actinomyces without the devel opment of actinomycosis of the lung or chest wall is an indi cation of the low virulence of these organisms In these cases the actinomyces did not behave differently from the general mixture of organisms involved in the putrid infection Two cases were cured by drainage alone and in the third good re sults followed additional use of penicillin and roentgen therapy

Apparently the actinomyces were carried from the mouth with a mixture of other bacteria which were responsible for the lung abscess Probably other factors in addition to simple inhalation are required to produce pulmonary infection by actinomyces

[A pirational infection of the lung is fairly common in elderly people and a variety of bacteria from the mouth and throat may be carried down Infected pyorrheal pockets seem to be the most common sources Cleaning up the mouth therefore is one way of guarding against such infections —Ed]

BRONCHIECTASIS BRONCHOLITHIASIS

Bronchiectasis in Childhood —*Clinical Survey of 160 Cases*—As the etiology of bronchiectasis becomes more clearly understood it should often be possible to prevent this disease Knowledge of the development and progress of the disease is still inadequate particularly in childhood when the first symptoms usually appear C Elaine Field[4] (London) studied 160 cases of irreversible bronchiectasis in childhood 67 in males and 93 in females No case was included in the study unless the diagnosis was confirmed by bronchogram or at autopsy (10 cases)

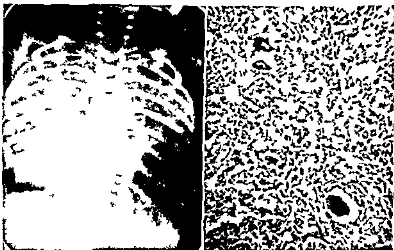
Symptoms appeared in the first year of life in about one fifth of the cases the number thereafter declining with ad vancing age In 55 6 per cent the history given by the parents associated onset of symptoms with pneumonia or pertussis The characteristic features of the disease included a constant cough with or without sputum this often being swallowed by children Hemoptysis was rare but in 33 1 per cent of cases there were associated asthmatic symptoms More children

(4) P d i 4 21 46 J ly 1949

or tubercles were not seen microscopically in any tissues other than the lungs

Gram stains of paraffin sections of the lung tissue showed numerous large hyphae and scattered spores Cultures produced a profuse growth of a green aspergillus in 48 hours The organism was identified in subcultures as Aspergillus fumigatus Fres

Coincident with this patient's illness a sister aged 7 also became ill with fever and rapid respiration A chest film was similar to that of her brother She was given penicillin streptomycin sul



F g 35 (left) —Ch st film of boy 5 sh w g d ff p l y filt t n
F g 36 (ght) —Se t n of l ng h w g g n l m to s infl m iato y (t w th g ant l
(Co te y f Il t g A J t l Ped t c 4 331 336 S pt mbe 1949)

fonamides and whole blood but showed no improvement and died five days later Autopsy was not done

Actinomyces in Putrid Empyema Coleman B Rabin and Henry D Janowitz[3] (Mount Sinai Hosp New York City) report three cases of putrid empyema secondary to rupture of putrid lung abscess in which in addition to the usual lung abscess flora anaerobic Actinomyces israeli (A bovis) was found in the pleural exudate In one case the pulmonary infection followed tooth extraction and in the other two there was advanced periodontoclasia with purulent gingivitis In one of these the actinomyces were found in the exudate about the gums

(3) J Th aci Su g 19 355 360 Ma h 1950

supports the theory that inadequate drainage of secretions is one of the predisposing causes of bronchiectasis

Massive collapse of the lung was associated with bronchiectasis in 46 3 per cent of cases Tubular dilatation was the commonest type of bronchiectasis It is important to recognize in children that bronchial dilatation may be reversible In diagnosis of irreversibility duration of the dilatation and its contour are helpful

Bronchoscopy did not prove helpful in diagnosis or localization of bronchiectasis Sedimentation rate was frequently raised but was of little help in assessing activity of the disease Alterations in blood count were few and usually significant only in severe active disease Complications were infrequent the commonest being pneumonia which occurred in 16 3 per cent of cases

[Various clinicians have implicated pulmonary collapse as a cause of bronchiectasis but it is doubtful whether collapse alone is the important factor Infection with destruction of the bronchial wall leading to its dilatation seems to be the commonest cause This of course may be favored or aggravated by bronchial obstruction The reversibility of true bronchiectasis is not conceded by many clinicians This study by Field is unusually interesting and thorough —Ed.]

Etiology and Pathogenesis Including Survey of 272 Cases of Doubtful Irreversible Bronchiectasis —According to Field[5] onset of symptoms of bronchiectasis commonly date from an attack of pneumonia or pertussis particularly in the first year of life Rubeola asthma and bronchitis are less commonly named Foreign body in the bronchus tuberculous hilar gland and removal of tonsils and adenoids are also predisposing factors The common factor in these conditions is nonaeration of some or all of the alveoli supplied by the bronchus This nonaeration resulting from either consolidation or resorption collapse from an obstructed air passage appears to be the essential factor predisposing to dilatation of the bronchus As long as there is a chance for the alveoli to reaerate the condition is reversible whether or not infection has occurred What if any is the time limit for this re expansion is not known Undoubtedly infection predisposes to permanent change but that it is an essential factor is unproved

Pulmonary collapse is therefore regarded as a prebronchiectatic state and in order to assess its importance two groups

(5) Ped t 4 231 248 A gu t 1949

were underweight than overweight for age and many had chest deformities Clubbing occurred in 43 7 per cent and *was diagnostic of irreversible bronchiectasis Physical signs* in the chest were variable but the most useful diagnostic find ing was localized rales on deep inspiration over the suspected area of lung Frequently children with bronchiectasis ap peared remarkably well if the disease was not too advanced or extensive The classic picture of bronchiectasis with cyanosis dyspnea gross clubbing fetid breath and quantities of foul smelling sputum is now comparatively rare in children

The incidence of pneumonia at all ages was strikingly high in children with bronchiectasis compared with normal children or those with nonpulmonary disease There was how ever no suggestion that bronchiectasis increased or decreased susceptibility to tuberculosis Sinusitis was frequently asso ciated with bronchiectasis but its exact relation remains obscure

In diagnosis roentgen findings are frequently inconclusive *unless confirmed by bronchogram Bronchography is* by far the most important diagnostic procedure and is an invaluable method of studying the development of the disease In con junction with the history and clinical signs diagnosis was suggested when linear markings or an opacity were seen in the roentgenogram Mottled opacities were less frequent and in five cases definite cystic areas were seen Usually the mark ings were fairly dense and coincided with the diseased area but occasionally this was deceptive when surrounding emphy sema obscured the linear markings or when the heart shadow prevented detection of left lower lobe disease Upper lobe *markings* were rarely noted because compensatory emphysema commonly occurs at the apexes Furthermore the most fre quently involved segment—the pectoral—gives the appearance of a hilar flare *rather than an upper lobe lesion in an antero* posterior view

In 85 6 per cent of cases the disease was in the left lower lobe and in 65 6 per cent in the lingula lobe *but in no case* was the lingula the only lobe affected The disease has a predilection for lobes whose bronchi are directed upward against gravity toward the main bronchus and those which have an anatomic peculiarity impeding drainage Both these conditions prevent proper drainage of secretions a fact which

prevention of bronchiectasis means prevention or better treat ment of the predisposing conditions particularly pneumonia pertussis pulmonary collapse and so called chronic bron chitis When cough persists after one of these conditions adequate convalescent care coupled with postural drainage and breathing exercises is advocated When bronchiectasis is established beyond doubt a choice must be made between three forms of treatment (1) A cure may be attempted by radical surgical removal of all diseased parts of the lung (2) Treatment may be purely medical with the aim of reliev ing symptoms (3) If the disease is too extensive for radical surgery excision of the more grossly diseased parts may be combined with medical treatment for relief of symptoms

In general radical surgical treatment is recommended in all cases in which an adequate amount of healthy lung can be preserved In skilled hands the operative mortality in children is low and with the reduction of complications by modern an esthetic methods and chemotherapy operative risks are mini mal Medical treatment which can be carried out at home at an open air school or at a convalescent home includes drain age breathing exercises and general health measures Chemo therapy for established bronchiectasis has so far been disap pointing Penicillin aerosol in a number of cases produced no lasting effect but more promising results have been reported with combined penicillin and streptomycin

Of 202 patients with proved bronchiectasis followed up to 10 years 109 were treated medically 13 were classified as cured Of 70 patients treated with complete surgical removal 27 were cured In both groups results were much better in patients without asthma Of 19 patients who died 9 had been treated surgically Ten patients classified as cured had bi lateral lobectomy

Serial bronchograms taken over the years revealed fre quent increase of dilatation in the anterolateral (pectoral) branches of the upper lobes in contrast to improvement or cure of the apical branches Varicose and fusiform types of bronchiectasis produced the least physical disturbance Al though clinically established bronchiectasis usually improved in the first two decades it is feared that deterioration may occur in the third and fourth decades The fact that after

of cases were studied (1) 272 cases of pulmonary collapse (2) 99 cases in which diagnosis of bronchiectasis was doubtful at first examination

Pulmonary collapse was seen most frequently in the right middle lobe and left lower lobe It was usually persistent in the left upper lobe but frequently the right lower lobe re expanded Duration of cough from the history was commonly three months or less in cases of pulmonary collapse that re expanded in contrast to two years or more in most cases in which bronchiectasis developed Of the 272 cases of pulmonary collapse in only 157 did the lung re expand without permanent bronchiectatic changes It was not uncommon however to find temporary bronchial dilatation in this group the bronchi returning to normal caliber when the collapse re expanded—a condition described as reversible bronchiectasis

Treatment recommended for pulmonary collapse includes steam inhalations postural drainage and breathing exercises Unless foreign body is suspected immediate bronchoscopy is not necessary No significant difference in incidence of re expansion of the lung was found between the cases treated with bronchoscopy and those treated without Of the 157 children with pulmonary collapse in whom bronchiectasis did not *develop* 111 were classified as cured *with no symptoms* or signs after three years observation 16 children were improved and 13 showed no change in general condition In these last two groups 23 children had asthma Six children mostly infants died from associated conditions and the rest could not be assessed accurately Field concludes that in most cases except those with asthma cure was effected

Diagnosis for 99 patients was doubtful bronchiectasis when they were first seen Of these 47 5 per cent had asthma a disease frequently difficult to differentiate from bronchiectasis In 40 true irreversible bronchiectasis developed after three or more years It was necessary to observe patients with doubtful bronchial dilatation over a period of years bronchograms being repeated at intervals to determine the permanently diseased parts

Prophylaxis Treatment and Progress with Follow up Study of 202 Cases of Established Bronchiectasis—Field[6] states that

(6) Pediatrics 4 355 372 September 1949

the incidence of *bronchiectasis* was 63 3 *per cent but in* those with predominantly exudative lesions it was 19 4 per cent *Bronchiectasis in reinfection tuberculosis* was *most* apt to occur after the first year of disease when the lesion had largely *lost its exudative quality Extreme* chronicity did not increase materially the chance for development of bronchiectasis Pred ilection *was shown for the* upper lobes and apical *ramifica* tions in lower lobes In contrast to bronchiectasis associated *with primary tuberculosis the* lingula *was frequently involved* and in general dilatations were confined to peripheral areas *without sharp limitation with respect to bronchopulmonary* segmentation In most cases bronchiectasis appeared so lim *ited in extent as to* have had little *bearing on* the clinical course

Unlike primary tuberculosis the factors leading to bron chiectasis in reinfection tuberculosis were less tangible Bron *chial occlusion intrinsic factors involving* the bronchial wall and extrinsic factors such as parenchymal lesions must be *considered*

[It is generally agreed that obstruction of a bronchus by a tuberculous lesion may lead to secondary destructive infection with permanent bron chiectasis However there is still much confusion with respect to changes in the bronchi related to uncomplicated parenchymal tuberculosis Some pathologists hold that under these circumstances true bronchiectasis is unusual and that the observed bronchographic defects can be explained as residual cavities or bronchial distortions due to fibrosis —Ed]

Pathogenesis of Bronchiectasis Roentgen Contribution. According to Felix G Fleischner[8] (Harvard Univ) bronchi ectasis is a condition characterized by a dilatation of bronchi Inflammation of bronchi lung and pleura and bronchostenosis play etiologic roles but loss of resilience of pulmonary parenchyma in pneumonia and emphysema and shrinking such as occurs with atelectasis and fibrosis provide the me chanical forces which dilate the bronchi Clinical manifesta *tions are determined by the type and severity of complications*

Deep necrotizing bronchitis may occur in respiratory in *fections particularly in children destroying bronchial* walls and leading to bronchopulmonary abscesses These if sta bilized may be relined with epithelium but *if so* are *not* bronchiectatic Dilatation of the bronchi is preceded and ac

(8) *R d l gy 53 818 835 D ember 1949*

lobectomy the remaining lung increases its functional capacity *in growing children makes it desirable to operate during* childhood

Relationships between Tuberculosis and Bronchiectasis Study of Clinical and Postmortem Material is presented by Edna M Jones W M Peck C E Woodruff and H S Willis[7] (Detroit Mun Tuberculosis Sanatorium) Bronchograms were obtained in 34 children whose mean age was 5½ years Lipiodol® instillation was carried out at a mean interval of 3½ years after x ray clearing of primary pulmonary tuberculosis Definite bronchiectasis was found in 24 in 20 there was evidence of bronchial obstruction for more than one year and in the remainder for less than one year Bronchi were obstructed less than a year in five and more than a year in five of those who had no evidence of bronchiectasis Bronchiectasis was distributed equally between the lungs It was localized in the anterolateral branch of the upper lobe bronchus in nine, in the apical branch of the lower lobe bronchus in four and in the middle lobe bronchus in four In every instance bronchiectasis occurred at the site of the previous primary tuberculosis Bronchiectasis tended to be coextensive with the bronchus and cylindric from root to periphery suggesting that anatomic or physiologic obstruction from endobronchial disease at or near the root or from enlarged tracheobronchial lymph *nodes may be responsible Symptoms either were associated* with the obstruction and primary complex (wheezing fever cough and thick sputum) or resulted from subsequent dilatation (recurrent colds fever cough copious expectoration or hemorrhage)

Postmortem bronchograms in 99 cases of reinfection tuberculosis showed bronchiectasis in 51 instances This diagnosis was substantiated by gross examination and histologic study in 46 All gradations of lesions were found between the extreme of complete bronchial obstruction with a resultant cavity surrounded by caseous material and collapsed alveoli and instances of typical bronchiectasis lined by stratified squamous *epithelium showing minimal obstructive* changes Most commonly tuberculous disease in the bronchial wall was extensive In case of predominantly fibrotic disease

(7) Am Rev Tuberc. 61 387 398 March 1950

to be settled. Overdistention of the lung does not seem to be a direct or important factor in pathogenesis since bronchiectasis has not been observed to develop after lobectomies or pneumonectomies when the remaining lobes or lung may be greatly distended The importance of identifying and treating infections particularly of a suppurative character is generally recognized —Ed]

Frontal Sinuses in Bronchiectasis Study on Morphologic Basis of Lung Disease is presented by Johan Torgersen[9] (Univ of Oslo) The frontal sinuses are smaller in many persons with bronchiectasis than in normal persons and were smaller in a group with congenital bronchiectasis than in a nonselected group Since roentgen abnormalities in the lungs were relatively slight in persons with congenital bronchiectasis examination of lungs and frontal sinuses may indicate the relative role of hereditary and environmental factors in the etiology of an individual case

In a previous article Torgersen dealt with the frequent occurrence of bronchiectasis in persons with situs inversus The most reasonable interpretation of these observations and those described in the present article may be that development of the upper and lower respiratory tracts depends on the integrative action of a complex of genes The manifestation of these genes depends on modifiers influencing the asymmetry of the viscera

Broncholithiasis Herbert W Schmidt O Theron Clagett and John R McDonald[1] (Mayo Clinic) report experiences with 41 patients Sex distribution was about equal and 71 per cent were aged 40 59 Symptoms varied from an unconscious raising of a small stone with a mild cough to severe stone asthma or bronchial colic accompanied by intense substernal pain and a sense of suffocation Multiple broncholiths were coughed up nonsynchronously by 19 patients Cough hemoptysis thoracic pain and fever were the commonest symptoms Physical findings were not diagnostic but depended on the size and location of the broncholith The roentgenologist suspected broncholithiasis in only three cases Probably the most diagnostic x ray sign was a dense area of calcium deposition at the apex of a triangular portion of collapsed lung

Bronchoscopic findings may be suggestive of tumor since often the broncholith is buried in a fleshy mass of granulation

(9) A ta d I 32 185 192 1949
(1) J Th S g 19 226-245 F bru ry 1950

companied by infection in most cases but is often mild and sometimes entirely absent Such findings do not in any way explain why bronchi become widened

In rare instances of rapidly developing complete bronchial obstruction with severe infection beyond it the secretion accumulating in the closed bronchi may contribute to bronchial dilatation by pressure from within However known physical and physiologic facts do not generally support the concept that secretion in the bronchi and differences of gas pressure within the bronchi and the surrounding parenchyma have a dilating influence

Loss of extensibility of the parenchyma occurring with patches of pneumonic consolidation or emphysema may cause an increased external dilating pull on the bronchi because of loss of the normally well balanced cushioning effect of the resilient parenchyma In atelectasis and fibrosis with shrinkage an outward contractile strain is added augmenting the pathologic traction on the bronchial wall Impairment of normal ventilatory expansion and collapse are the basic mechanical disturbances common to these conditions In the early phases the dilating conditions are reversible and when they disappear dilated bronchi may return to normal This concept of the cause of bronchial dilatation explains most of the clinical and morphologic features of bronchiectasis and is well supported by x ray and histologic observations

In treating bronchiectasis the main effort should be prevention of crippling deformity of the bronchi Infection must be combated and residual atelectatic areas reventilated after any respiratory infection especially in childhood X ray evidence of persistent atelectasis even in small areas should encourage use of bronchoscopic aspiration and any other measure to prevent the condition from becoming chronic If respiratory infection is treated effectively pleural and pulmonary complications are recognized early and foreign bodies and bronchial tumors promptly removed the incidence of permanent gross bronchial deformity will be reduced Instances of chronic suppurative disease with extensive bronchopulmonary damage requiring surgery will become less frequent

[It is interesting to read this point of view on the factors involved in pathogenesis of bronchiectasis indicating that the question does not eem

to be settled Overdistention of the lung does not seem to be a direct or important factor in pathogenesis since bronchiectasis has not been observed to develop after lobectomies or pneumonectomies when the remaining lobes or lung may be greatly distended The importance of identifying and treating infections particularly of a suppurative character is generally recognized —Ed.]

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tissue When this tissue is removed by forceps the broncholith may be felt or seen Biopsy is extremely important since broncholiths may occur in association with bronchogenic carcinoma Once the broncholith is removed the bronchial mucous membrane usually returns to normal In 17 cases the broncholith was either found and removed or coughed up immediately after bronchoscopy Hemorrhage or pneumothorax may occur after bronchoscopy but is not usually serious

When the broncholith is in a part of the bronchial tree that cannot be visualized by the bronchoscopist the problem is that of an indeterminate bronchial lesion In such cases early exploration is safest since a large percentage of these lesions have turned out to be bronchogenic carcinomas and not broncholiths If a broncholith is found segmental resection lobectomy or pneumonectomy may be necessary depending on its location In this series it was necessary to remove all or part of a lung in 10 cases There were no surgical deaths Broncholiths may arise from calcified or ossified lymph nodes calcified or ossified elastic cartilage of the bronchi or metastatic pulmonary calcification Of the 10 cases in which the lung was available for study ossified or calcareous cartilages were present in 9 and ossified or calcareous nodes in 5 in 1 there was no calcific change in either the cartilage or the lymph nodes

Bronchoscopic removal or surgical resection usually relieves symptoms

Active Bronchopulmonary Lithiasis Eugene Freedman and James H Billings (Cedars of Lebanon Hosp Los Angeles) report seven cases of active bronchopulmonary lithiasis six were proved by surgery and histologic examination and in the seventh the stone were expectorated This raises to 103 the total number of cases reported in the American and English literature since 1900

Broncholiths may develop outside the bronchi in any thoracic organ which has been the site of necrosis or inflammation followed by calcification Subsequently the stones may perforate into the air passages When forming within bronchi broncholiths may originate from anthracotic or silicotic material inspissated secretions fibrous plugs soft tissue se

(2) R d l gy 53 203 215 A gu t 1949

questra or foreign bodies Salivary calculi rhinoliths tonsil liths or spicules of bone loosened during surgery on the sinuses or nose may be aspirated and become broncholiths Usually broncholiths are due to perforation of calcified tuberculous lymph nodes

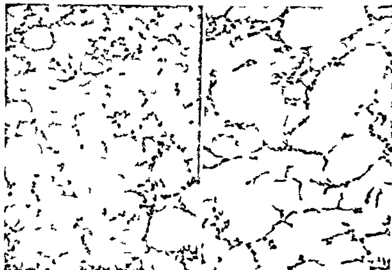
Most broncholiths are from 2 to 20 mm in diameter and are grayish or brownish white Their surfaces may be smooth irregular or mammillated and they are occasionally enclosed in a fibrous capsule They may be solid or laminated and may even contain a liquid center They are composed of 10 15 per cent calcium carbonate and 85 90 per cent calcium phosphate

The clinical picture may vary from absence of signs or symptoms to those of a severe illness The manifestations are manifold and depend greatly on the degree of obstruction and secondary inflammatory changes distal to the obstruction Cough is usually paroxysmal first dry then productive Pain is frequently localized in the parasternal area Hemoptysis is frequent particularly after expulsion of the stone Fever chills leukocytosis and anemia may be present Bronchorrhea is caused by increased goblet cell activity in the irritated mucosa

Bronchoscopy may reveal the broncholith within the bronchi or arouse suspicion of a perforating calculus by revealing an ulcerating or granulomatous lesion in the bronchial wall However even in the presence of a negative biopsy carcinoma is the condition most commonly suspected Conclusive diagnosis is not possible on the basis of x ray findings These may suggest carcinoma of the lung chronic lung abscess chronic bronchiectasis with atelectasis chronic pneumonitis or fungoid disease Laminagraphy is an important diagnostic aid for it may show the stone in the bronchial lumen or demonstrate it in close relation to the bronchial wall with secondary inflammatory changes peripheral to the point of obstruction

The broncholith is often expelled spontaneously with characteristic relief of symptoms Removal of broncholiths by bronchoscopy is not without risk of pneumothorax mediastinal emphysema and hemorrhage Lobectomy or pneumonectomy may be required The plan of treatment must be based on the type of pulmonary and vascular complications secondary to the bronchial obstruction infection or hemorrhage

Local Organ Hypersensitivity to Autogenous Antigens Experimental Production of Pneumonitis was achieved by Richard Jahiel and Rene Jahiel [a] (Columbia Univ) Lungs of young mature rabbits were sensitized by a single trans thoracic injection of a small amount of hydrolyzed autoserum



F g 37 (l ft) —R ght l ng f rabb t e s t d w th 0 5 cc hyd ly ed a to-serum. Shock oj ction of 2 cc g x we ks l te Rabb t kill d 48 h rs ft r w ds N t al eol edem
F g 38 (ght) — l ght e t n l ft l g of th m bb t
(Cou te y of J h l R and J h el R J All gy 21 102 119 Ma h 1950)

autogenous urine or saline extracts of homologous liver or autogenous skin Two to 10 weeks later a shock injection of the antigen was given intravenously Then the rabbits were examined over a period of 1 96 hours

Control animals received only intrapulmonary sensitizing injections Focal congestion and edema which developed in the lung disappeared in 10 15 days Controls which received only intravenous injections had no tissue reactions Those in which the sensitizing injection was given subconjunctivally in

(2a) J Alle gy 21 102 119 March 1950

the vitreous humor or in the brain developed lesions in these organs after the shock injection but no pulmonary lesions

Previously sensitized animals which received an intravenous injection of the same antigen after a suitable time interval developed lesions in the sensitized lung during the first hour which were still present 96 hours later The severity of the lesion was not appreciably influenced by the time interval between the two injections when it was varied between 2 and 10 weeks Lesions obtained with exogenous antigens were identical to those obtained with endogenous antigens Grossly there were areas of congestion and edema which involved a portion of a lobe to as much as the entire lung depending on the severity of the reaction Microscopically lesions were located mainly in the blood vessels and alveoli Capillaries in alveolar walls were congested and alveolar spaces contained edema fluid (Figs 37 and 38) Vascular lesions consisted of endothelial reaction endarterial and periarterial edema and periarterial infiltration with eosinophilic cells and small and large mononuclears The pneumonitis was interpreted as an allergic vascular reaction of the lung involving relatively large vessels arterioles venules and alveolar capillaries

These experiments suggest that partial hydrolysis of autogenous protein tissue destruction and liberation of endocellular material and reabsorption of an excretory product may give rise to autogenous allergens which cause changes in previously sensitized tissue Such mechanisms may play a similar role in man

Parenteral and Aerosol Administration of Antihistaminic Agents in Treatment of Severe Bronchial Asthma Hyman J Rubitsky Elliott Bresnick Leon Levinson George Risman and Maurice S Segal[3] (Tufts College) used diphenhydramine and tripelennamine to treat 15 patients with severe bronchial asthma which was refractory to conventional therapy Clinical improvement occurred in 10 as a result of significant relief from bronchospasm or prompt restoration of epinephrine sensitivity following intravenous administration of antihistamines The most favorable results were obtained in those who were histamine sensitive during protection studies The poorest results were obtained in those with obstruction of the

(3) N w E gl nd J M d 41 853 859 D 1 1949

tracheobronchial tree by inspissated mucus plugs in elderly patients with significant and irreversible cardiac and pulmonary disease and in histamine insensitive persons

DOSAGE—Doses ranged from 20 to 50 mg of either agent and were administered at a rate not exceeding 10 mg/minute To avoid chemical incompatibility the drugs were not mixed with solutions of aminophylline After relief of severe bronchospasm patients may be maintained during convalescence with antihistamines administered by aerosol or rectal routes as supplements to other therapy By the aerosol route 2 5 per cent tripelennamine solution either alone or mixed in equal parts with a bronchodilator may be administered in a Vaponefrin nebulizer For rectal instillation 25 50 mg capsules of diphenhydramine may be used puncturing the ends of the capsule before insertion Either drug may be administered rectally in solution

The most common side reactions were drowsiness and dizziness particularly in the upright position but they disappeared gradually in one or two hours Headache transient chilliness nausea fatigue palpitation pallor blurred vision tachycardia and the alert reaction were observed most frequently

Treatment of Status Asthmaticus Richard A Kern[4] (Temple Univ) states that the best treatment is prevention by complete diagnosis and thorough treatment of asthma complications Anything less than complete and lasting relief does not merit satisfaction

TREATMENT—The patient should be immediately hospitalized in a private room The bed should have foam rubber pillows and mattress and cotton or woolen blankets should be covered with cotton sheets There should be no rugs no upholstered furniture no flowers and the room should be provided with filtered air if possible Freshly painted rooms and insecticidal spray should be avoided Relief from asphyxia is paramount and may be accomplished by oxygen given by mask or intranasal catheter For economy oxygen in helium is best given in a tent When the patient is cyanotic and obviously unable to cough up sputum bronchoscopy should be performed promptly Administration of 0 5 cc epinephrine a minute before the bronchoscope is passed or even while it is in situ stimulates secretion of a thinner mucus that can be more readily aspirated During the whole procedure 100 per cent oxygen can be given through the bronchoscope

(4) Po tg d M d 7 40 44 J n y 1950

The patient desperately needs rest and this is best achieved by induction of surgical anesthesia. Avertin* is preferred since it is nonirritating and easy to give by rectum in a dose of 60 80 mg/kg body weight Ether is second choice and when administered rectally should be given in doses of 150 200 cc of a mixture of equal parts ether and olive oil mixed with an egg beater For a child aged 12 the dose is 100 cc. It should be given slowly 1 2 drachms at a time into a cleansed bowel 20 minutes being required for the whole adult dose Since ether is eliminated in the lungs it may cause irritation of the bronchial tubes

Wet lungs are occasionally seen and may be treated by venesection Removal of 250 cc blood rapidly does more good than removal of 500 cc slowly Hypertonic glucose solution given intravenously (50 100 cc of 25 per cent solution or 25 50 cc of 50 per cent solution) may be helpful in such cases

Frequently the patient is dehydrated and starved If the blood sugar level is below 80 mg/100 cc 1 000 cc of a 5 per cent glucose solution should be administered by slow intravenous drip Salt solution should not be given Total fluid intake should be 2 2 5 L daily Intravenous administration is stopped when oral intake is adequate Epinephrine may be given to advantage intravenously in the glucose infusion 2 cc of 1 1 000 epinephrine in the first 60 cc of infusion requiring 30 minutes to run in Thereafter the rate of administration should be only half as fast If given intravenously or parenterally epinephrine should be administered at the rate of 1 minim/minute and never more than 1 minim at a time When epinephrine fails slow intravenous injections of aminophylline may be effective For adults the contents of one ampule containing 0 5 Gm in 2 cc of solvent are diluted to 10 cc with normal saline and injected evenly over 20 minutes For children the dose is 0 006 Gm/kg body weight Doses may be repeated every six or four hours In less severe case or when the attack begins to yield aminophylline may be given rectally either in a suppository or 0 5 Gm dissolved in 30 cc tap water as an enema Papaverine relaxes smooth muscle spasm but does not depress the cough reflex but it must be ascertained that the patient is not ensitive to opium or its derivatives before it is administered Morphine pantopon* dilaudid* codeine and other opiates should never be used in status asthmaticus nor should antihistamines be used

Since infection plays an important etiologic role penicillin can be started promptly in most cases but not before a suitable pecimen has been delivered to the laboratory for culture of bacteria and determination of drug susceptibilities If the patient is known to be

sensitive to penicillin or any other antibiotics they should not be used.

Improvement in an attack of status a thmaticus is heralded by better and more lasting effect of epinephrine increased quantity of a thinner sputum and subsidence of fever It may occur gradually or with dramatic speed In less severe but persistent cases of asthma nonspecific protein shock therapy may be used The initial dose of vaccine is 10 25 million typhoid bacilli repeated for as many as three or four doses with an interval of five days between injections For best results the fever must rise to 102 104 F and doses may be doubled or further increased to achieve uch a fever Nonspecific fever therapy must not be substituted for specific treatment and should be reserved for patients in whom avoidable causes of asthma cannot be found

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PNEUMOCONIOSIS

Determination of Range of Particle Size in Silicogenous Dust.—*Presentation of Problems*—H Gessner J R Ruttner and H Buhler (Zurich) state that intense silicogenous properties are generally attributed to quartz dust but not always to the other silicic acid modifications and the silicates regarded by most investigators as actually less silicogenous In this study silicogenous dust means not only quartz but also silicates Dust inhalation is presupposed in the development of silicosis particles over a certain size cannot be inhaled or are stopped in the upper air passages by the physiologic defense mechanism All authors agree that only particles under 10 μ are injurious but opinions vary as to minimal size of injurious particles and are based on guesses The question can only be decided by examination of the dust deposited in the lungs

Several specimens of lungs from deceased silicotic patients were available Before examination of the dust particles some portions of dried lung weighing 2-4 Gm were used to determine total ash content and the portion of ash that was insoluble in hydrochloric acid To avoid sintering of the particles in the incandescent method which would have falsified the results of the intended elutriation analysis the dust ma

(5) Schw m d W hn 1 79 1241 1 45 Dec. 24 1949

terial was isolated from the tissue by dissolving the fat and oxidizing the insoluble parts with H O in sulfuric acid solu tion and with nitric acid the silicogenous component re mained in the test material while the nonsilicogenous com ponents disappeared The authors stress the necessity for *systematic examinations* of the ash and dust contents and their variations in each portion of the lungs to show the rela tions between the anatomic changes and the migration and distribution of the inhaled dust in the lung

Results of examination of individual specimens were shown in protocol extracts which included information about the place of employment the rock present there and it chemical composition duration of exposure of the subject and the anatopathologic diagnosis the findings of crystaloptic roent gen and orienting chemical examinations the results of elu triation analyses

Evaluation of Results —Gessner Ruttner and Buhler[6] show that the total ash content in their six cases agreed particu larly well with the findings of Gardner and Redlin for a much larger group The silicic acid content of the ash from lungs of three patients with severe silicosis was about 50 per cent of the total ash This average differs considerably from the American average (19 87 per cent) but remains within the total American variations of 0 33 and 62 79 per cent The three silicotic patients died with an average of 5 9 per cent of silicon dioxide while the corresponding average for the American group was 2 19 per cent The extreme values of the three ex amined patients are 2 8 and 8 8 per cent which are well within those given by Gardner and Redlin (0 02 and 15 43 per cent)

The particle distribution curves of the three cases showed a maximum in the range of 0 9 1 0 $\mu\Phi$ The proportion of larger particles was 60 70 per cent that of smaller particles 30-40 per cent The larger particles found were about 20 μ in diameter in only a small percentage were particles between 10 and 20 μ The question of how particles under 0 5 $\mu\Phi$ behave in the lung cannot be evaluated from the authors investiga tions because the curves for this range were uncertain how ever the percentage of particles of this size in the dust is always low

Results of this study show that the composition of par

(6) S hw med W h sch 79 1 58 1262 Dec 31 1949

ticles in the dust reaches a maximum in the range of 1 μΦ and that with increasing size fewer particles are retained in the lungs In the range of 10 20 μ deposition in the lungs stops because the particles are arrested in the upper parts of the bronchial tree In the technical examination of industrial dust to evaluate the danger of silicosis it is imperative to deter mine the quantitative participation of fine particles This re quires determination of the total concentration of the dust (weight of dust/unit of volume of dust containing air) and of its particle composition in addition the chemical and mineralogic composition and especially the quartz content must be studied

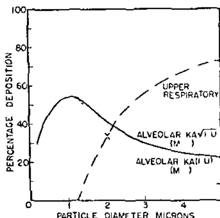
Measures to combat dust must take into consideration the finest particles A ventilating system which exhausts the dust containing air and blows in fresh uncontaminated air is best The use of water to precipitate dust during its formation (wet boring or polishing) is relatively less effective for fine than for large particles but the decrease of fine particles in the air is still considerable Precipitation of dust already in the air by water sprinkling is generally inefficient The commonly used separators are efficient only for certain particle sizes and the critical limits are usually over 5 10 μΦ rarely under this The result is continuous accumulation of the fine par ticles in the air

[Interest is increasing in the effects of extremely fine particles of dust which may be inhaled e pecially in certain occupations This obviously is important not only in providing for dust control but also in helping to explain the variety of pathologic changes which may be induced in the lungs —Ed]

Influence of Particle Size on Retention of Particulate Mat ter in Human Lung was studied by J H Brown K M Cook F G Ney and Theodore Hatch[6] (Univ of Pittsburgh) Size is a primary factor in determining the magnitude of the hazard associated with inhalation of particulate matter In this study retention was calculated by direct measurement of the amount of dust returning from the respiratory system in the exhaled air as in the standard procedure for measuring total retention Each exhalation was separated serially into several fractions representing air from the upper respiratory tract midportion and alveoli and the amount of dust in each was determined It was possible to calculate the true lung air

(6) Am J P b He lth 40 450 458 Ap 1 1950

in each fraction and the outgoing concentration of dust in upper respiratory air and in lung air From these values and the intake concentration the total retention the one way up per respiratory retention total retention from upper respira tory air and alveolar retention were calculated Essential equipment consisted of a face mask connected to a rotary valve with eight ports for delivering dust laden air and col lecting samples The valve was electrically operated through



F g 39—P tage d pos t on f hal d d t th pp p t y t t d l l m l t t p t l ze (Cou t y f B w J H et l Am. J P b Health 40 450 458 Ap l 1950)

a relay panel and commutator which was connected by a di rect mechanical drive to a Drinker respirator in which the person was placed

In over 100 tests with median particle size ranging from 0 24 μ to more than 5 μ total retention decreased systemati cally from 90 per cent or more for particles 5 μ or greater to 25 30 per cent for 0 25 μ particles Upper respiratory reten tion also decreased in an orderly fashion reaching zero at a finite particle size above 1 μ Alveolar retention remained at 90 100 per cent for all sizes down to about 1 μ then de creased in proportion to total retention

The percentage of inhaled particles deposited in the up per respiratory tract and in the alveoli were calculated (Fig 39) The alveolar curve is based on the assumption that upper

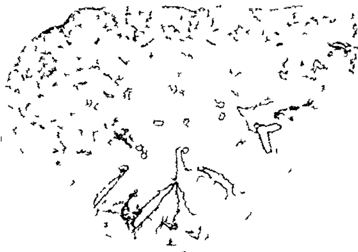
respiratory retention is equal in both directions For comparison another alveolar curve (dotted line) is given based on assumed one way upper respiratory retention One represents maximal and the other minimal alveolar deposition in relation to particle size The true relationship lies between these two limits Both curves show that for mineral particles the optimal size for alveolar deposition is about 1 μ On a ratio basis probability of deposition is about the same for larger and smaller particles

[Technics of this description are useful in study of the penetration and retention of dust in the lungs and inferentially throw some light on the adequacy of the defenses of the respiratory tract against such penetration —Ed]

Deposition and Fate of Plutonium, Uranium and Their Fission Products Inhaled as Aerosols by Rats and Man. Kenneth G Scott Dorothy Axelrod Josephine Crowley and Joseph G Hamilton (Univ of California) observed the rats in metabolism cages killed them at varying times after exposure to the aerosols and assayed the urines tissues and feces using a Geiger Muller counter and radioautographic technic Particulate material 1 μ or less in size composed of plutonium or uranium or their fission products which include a large series of elements in the central region of the periodic table were deposited in lung alveoli and in respiratory passages lined by ciliated epithelium as evidenced by radioautographs (Figs 40 and 41) Despite the different origin chemical and physical natures of the fissionable and fission products their deposition and elimination were comparable In regions equipped with ciliated epithelial cells almost complete removal of the active particles occurred in a matter of hours but in the alveoli removal of any large percentage of the aerosol required many months Removal was primarily via the bronchial tree and there was no evidence that significant portions were removed by the lymphatic system or blood vessels

The material excreted by the bronchial tree could be detected in the fecal fraction of the excreta Though plutonium and most of the fission products were not absorbed in the gastrointestinal tract recent products of fission such as Ba^{140} Sr^{89} and Sr^{90} were absorbed in amounts of 5 60 per cent of the total given Of the absorbed portion 64 per cent was found deposited in bone The low bone deposition suggests that the

(7) Ar h P th 48 31 54 J ly 1949





F g 40 (t p) —L g ect h w g p lmon ry d po tion f pl t m x d os l obta ned by b g p) to m bl d d pl ton m t t Th t w k ll d 10 m t ft po l l t m h ly d p t d on l ted b n bial f nd n l enl × 6

F g 41 (bott m) —R d tog ph f l g ct on × 6

(Court y f S tt K. G t al A h P th 48 31 54 J ly 1949)

fission products were locked in insoluble particles when administered as aerosol

[This is an ingenious method of demonstrating the deposition of particulate matter inhaled through the respiratory passages The speed and efficiency with which the ciliary apparatus operates is most remarkable, indicating its prime importance as a defensive mechanism Retention of particles in the alveoli for prolonged periods is assumed to be a factor which is largely responsible for inflammatory and fibrotic changes occurring when the material has irritating qualities —Ed]

Aerosols Effect of Saline Aerosols on Dust in Atmosphere, Reduction of Dust Deposition in Lungs by Saline Aerosols L Dautrebande B Highman W C Alford F L Weaver and E C Thompson[8] (U S Pub Health Service) have found that saline aerosols with a mean micellary diameter of less than 0 5 μ can effectively coat and agglutinate dust particles of similar size suspended in the atmosphere To determine the effect of saline aerosols on deposition of dust in the lungs rabbits were exposed for five hours to air mixed with dry willemite dust Another series of rabbits was simultaneously exposed under identical conditions to a similar dust mixed with saline aerosol instead of normal air

Rabbits exposed to the untreated dust generally became sluggish after two hours whereas those exposed to dust treated with saline aerosol remained active even after five hours exposure and showed much less dust in their lungs The first reaction to dust inhalation was short shallow respiration leading to tachypnea Respiratory rate of rabbits exposed to dust alone exceeded 180/minute whereas that of those exposed to dust with aerosol was about 135/minute. This difference would be even greater if from the third hour on rabbits subjected to dust alone did not exhibit a certain degree of decompensation of the respiratory centers

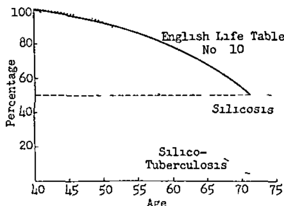
Examination showed less pronounced lung changes in the group receiving saline aerosol Dust tended to accumulate at bifurcations of the bronchi and alveolar ducts along surfaces facing the inspiratory current and in the alveoli particularly near the hilus and adjacent subpleural areas When aerosol was not used the lungs often showed many scattered atelectatic areas and the lumens of many bronchi and bronchioles appeared obstructed by exudate intermingled with dust With aerosol these changes were either absent or greatly reduced

(8) O cup Med 5 506-521 May 1948.

Examination of the lungs of animals killed at varying periods after exposure indicated that the dust deposits particularly in the bronchi disappeared after a shorter rest period in the group exposed to the aerosol treated dust

[This is a promising approach to the question of dust control As indicated in the study of Gessner Ruttner and Buhler (p 263) the mere spraying of the air with water may carry down large particles but often leaves finer more harmful particles suspended Some more efficient method therefore is urgently needed —Ed.]

Mortality and Survival Rates in Males with Silicosis or Silicotuberculosis The group studied by H Midgley Turner and W J Martin[9] (Sheffield Univ) consisted of 814 men



F g 42—P entag f or f om g 40 il cos d l t b l (C t y f T H M and M t W J B t. M J 2 1148 1150 Nov 19 1949)

348 with silicosis and 466 with silicotuberculosis all of whom had reached age 40 Survival rates at ages over 40 for silicosis and silicotuberculosis together with those for the male population are shown in Figure 42 Only 23 cases were first diagnosed as pure silicosis and later as tuberculosis Death occurred in 610 15 cannot be traced and the remainder are living

The ratio of silicotuberculosis to pure silicosis varies in different trades Of 521 grinders 63 per cent had silicotuberculosis whereas of 63 coal miners only 37 per cent had silicotuberculosis Clinical experience supports the view that in comparable cases prognosis is better for coal miners than for

(9) B t M J 2 1148 1150 N 19 1949

grinders it is suggested that the presence of iron in the lungs may have an unfavorable effect on local tissue resistance to tuberculosis

A disadvantage in treatment of silicotuberculosis is that collapse therapy is rarely either indicated or helpful because of the patients ages the almost invariable reduction in cardio respiratory capacity due partly to concomitant emphysema and the difficulty in judgment of the functional capacity of the contralateral lung In men over 50 with silicosis decreased resistance to respiratory infection and the effects of emphy sema and bronchitis on cardiorespiratory function are im portant factors influencing mortality Death from causes other than tuberculosis occurred in 297 patients In 11 per cent death was caused by cancer of the lung Of these 19 occurred in grinders indicating that inhalation of metal dust may be of more importance than inhalation of silica in etiology of cancer

[This study appears to be highly significant Up to a certain point silicosis does not cause much functional disturbance Then there may be a rather abrupt and rapid development of disability often related to sim ple respiratory infections to which the silicotic is especially susceptible Subsequently the bronchitis often becomes chronic leading to ventilatory difficulty and increased di ability The potentialities of silicosis therefore are serious because of the greater susceptibility to infection whether tuberculous or otherwise —Ed]

"Egg Shell' Calcifications in Silicosis Charles E Gray son and Helen Blumenfeld[1] (Stanford Univ) observed char acteristic calcium densities of unique morphology in the chest x rays of 40 of 200 silicotic men These shadows appeared as circular or oval rings in the hilar or mediastinal regions and there was faint stippling throughout the enclosed tissue Those with calcification had an average of five years less total exposure to silica and a two year longer interval since the beginning of exposure This suggests that the milder cases of silicosis occur in those who live longer and therefore deposit calcium many years after the original exposure Sixty per cent of those with calcification and 49 per cent of those without cal cification had no evidence of tuberculosis

Eight patients had a history of exposure to silica and x rays showed shell calcifications and nodular pulmonary densities Silicosis was confirmed by autopsy there was no histologic or clinical evidence of chronic pulmonary infection

(1) Rad l gy 53 162 6 A g t 1949

These findings were regarded as proof of the relation between silicosis and egg shell calcifications Figures 43 and 44 show the typical gross and x ray appearances of such lesions There were no similar findings in lung ti sue Apparently cal cium deposition begins diffusely throughout the node but



F g 43 (l ft) —T s t d m d st nal nod s
F g 44 (ght) — Roe tg nog m f malle nod mm sed w
(Cou t y f Grayson C E d Et m nf ld H P l l g 53) o
A g t 1949)

later becomes more prominent beneath a heavy capsule that forms around the node

[Pathologi ts wl o have had long experience with silicosis are familiar with the diffic ulty of proving wh ther or not there are sociated changes due to fibroid tuberculo is Though the presence of hell like shadows of calcific dens ty in the lymph nodes is highly suggestive of silicos s par ticularly when they are numerous and bilateral it seems prob ble that at least some of them and perhaps a majority are related to associated infection especia y tuberculosis which has become p rtly or completely healed Th s tudy is objective and k eps aliv the interest in an important problem —Ed]

Morphology of Bauxite Fume Pneumoconiosis J P Wyatt and A C R Riddell[2] (Toronto Ont) report six fatal cases of this disease which is caused by exposure to intense

(2) Am J P th 25 447 465 May 1949

concentrations of amorphous alumina dust during the manufacture of corundum During the processing of a mixture of bauxite iron and coke in electric furnaces dense white fumes are evolved which lead to contamination of the furnace rooms All fatal cases have occurred in furnace feeders or cranemen

The common clinical findings are shortness of breath cyanosis substernal discomfort and recurrent episodes of spontaneous pneumothorax from rupture of emphysematous



F g 45—Alveola wall w ll n a d th k n d by m le ells d fib bl t c n l and c p ll ry p thw y s l lte t d × 450 (C te y of W y tt J P a d R dd ll A C R Am J P th. 25 447 465 May 1949)

bullae Chest x rays show diffuse irregular lacelike and granular shadows greatly increased width of the mediastinum and lung collapse

Analysis of furnace fumes and patients lungs show that both contain significant amounts of amorphous silica and alumina thus offering a close chemical correlation between cause and effect

Grossly the lungs were gray and of relatively normal size on palpation a diffuse widespread induration was noted The size nodulation configuration and granite like character of a silicotic lung was lacking Many large emphysematous vesicles were seen The hilar and tracheobronchial lymph nodes were

not enlarged hard or nodular Microscopic examination of the lungs showed that initially there was intracellular septal edema with early fibroblastic proliferation (Fig 45) Next there was infiltration of inflammatory cells and fibroblastic proliferation was succeeded by collagen deposition The fibrosing septal walls either remained distinct or became massed together and produced wide bands of scar (Fig 46) Obliterative endarteritis was most pronounced in the regions of diffuse



F g 46—Dense b da d t b f ld t u d mphy m t p kets × 1 0 (C te y f Wy tt, J P d R ddl A C R Am J P th 25 447 465 M y 1949)

fibrosis There was no evidence of any specific granuloma or sarcoid The tissue reaction did not resemble any previously described process Because of the nature of the history and other findings none of the other pneumoconioses need be considered though in some of the scarred areas doubly refractile particulate matter was demonstrated by Polaroid examination

It is suggested that the mechanism is that of an amorphous dust which evokes a rapid sclerosing process in the pulmonary septa and interferes with the koniophage transmission mechanism usually responsible for dust elimination The

resultant diffuse interstitial fibrosis with absence of nodule formation is probably due to inhalation of amorphous alumina dust though the significance of the simultaneously inhaled amorphous silica has not been completely evaluated

[Identification of this type of pneumoconiosis differing in many respects from classical silicosis opens the field for further investigation of the effects of extremely fine dust It is especially important to recognize that with this disease functional disability appears more rapidly and is of greater severity than with the more familiar nodular silicosis in which lesions are more discrete and fibrosis in the alveolar septa is less diffuse Probably in time some fibroses loosely diagnosed as sarcoidosis will be found to be related to the inhalation of unusual dusts—Ed]

Acute Dermatitis and Pneumonitis in Beryllium Workers Review of 406 Cases in Eight Year Period with Follow up on Recoveries In the series studied by Joseph M DeNardi H S Van Ordstrand and Morris G Carmody[3] dermatologic manifestations occurred in 195 men and 211 displayed major respiratory tract manifestations Of the latter group 121 had tracheobronchitis and 90 chemical pneumonitis Chemical nasopharyngitis invariably preceded these lesions but frequently occurred independently Pneumonitis is the severest form of this industrial disease and 10 patients with this reaction died

The cause of berylliosis has not been established in the plant atmosphere the sulfate and halide radicals and their acids are in relatively greater atmospheric concentration than beryllium In some cases magnitude of exposure was apparently related to occurrence and severity of the disease but in others no such relation could be established Individual sensitivity also contributed to the occurrence and severity of the disease X ray and clinical changes result from irritation arising from the presence of and ensuing reaction to inorganic salts of beryllium in the bronchioles or histamine like by products which cause spasm and partial block of the finer respiratory conduits Exchange of gases in the alveoli is slow resulting in local anoxia which in turn disturbs the colloidal balance in tissues and causes fluids to pour into the alveoli producing edema

The two main types of pneumonitis are the fulminating and the insidious The former is least common and usually is associated with brief exposure to anhydrous beryllium sulfate fumes Symptoms may appear in a few hours or as late as 72

(3) Oh Stat M. J 45 567 575 Ju e 1949

hours after exposure and comprise spasmodic cough chest tightness with substernal pain severe exertional dyspnea and in severe cases cyanosis Physical examination reveals acro cyanosis decreased vital capacity limited chest expansion and sibilant rales With adequate care recovery usually occurs within 7 16 days

The insidious type of pneumonitis usually follows pro longed exposure to the fumes or dust of beryllium sulfate tetrahydrate beryllium chloride or beryllium oxide and prob ably results from cumulative irritation of the bronchioles by small amounts of the compounds Symptoms include dyspnea on mild exertion spasmodic cough substernal burning pres sure or pain with tightness in the chest general weakness anorexia and weight loss There are drop in vital capacity acrocyanosis fine to coarse rales rapid pulse and increased respiratory rate temperature is normal unless there is sec ondary infection Complete recovery may require 4-12 weeks

X ray changes in the lungs seldom occur in either type until one to three weeks after onset of symptoms and physical findings Typically peribronchial haziness and punctate in filtration are scattered throughout the lower half of each lung field Treatment for both types consists of hospitalization and intermittent use of oxygen as indicated During the last six months penicillin and the antihistaminic drugs have been given with gratifying results in relief of respiratory distress and spasmodic cough and perhaps have shortened the course of the disease

Recent re examination of 20 persons who had the severer type of pneumonitis revealed no recurrent or chronic manifes tations of the disease and no resultant disability

[The pathogenesis of pulmonary disease following beryllium exposure is till obscure As explained here the mechanisms involved in acute reactions appear relatively simple The granulomatous form of reaction is not understood and there is still a question whether complicating infec tion or some other chemical factors may be involved —Ed]

Fate of Oil Particles in Lung and Their Possible Relation ship to Development of Bronchogenic Carcinoma is discussed by L R Sante[4] (St Louis Univ) He reports two cases of bronchogenic carcinoma in one of which the growth un doubtedly arose in pre existing paraffinomas In the other lipoid pneumonia was present but the etiologic relation to the malignant lesion was less definite

After vegetable oil is introduced into the lung that re maining in the bronchial branches is coughed up and expec torated leaving feathery deposits of oil in the alveoli For eign material in the air sacs cannot be removed by coughing or ciliary action but only by the action of phagocytic cells Microscopic examination shows enormous macrophages sur rounding and engulfing oil droplets There is little if any in flammatory reaction probably because vegetable oils are com pletely free from fatty acids Deteriorated oils should not be used because the fatty acids may result in irritation and lung damage

Animal oils such as cod liver oil cause a mechanical re sponse similar to vegetable oil in the bronchial tree but once they reach the alveoli they remain for long periods before being effectively removed by phagocytosis During this time oxidation and deterioration occur The oil becomes stringy and sticky and large amounts of fatty acids are formed An intense inflammatory reaction and extreme fibrosis results There is pronounced cellular infiltration of the surrounding lung structures and large multinucleated foreign body giant cells appear Clinically the findings may be those of pneu monia Severity of the lipoid pneumonia is influenced by the quantity of animal oil amount of fatty acid and bacterial infection

Once mineral oil enters the alveoli it is questionable whether it is ever eliminated Since it is an inert material in capable of saponification it resists all efforts of phagocytes to digest it It may be carried with little change via the lym

(4) Am. J Roentg vol. 62 788 797 Dec mber 1949

phatics to the hilus There is an extreme degree of cellular reaction which results in fibrosis and dense almost acellular scar tissue Phagocytic cells may be destroyed by the indigestible oils which they contain A mass of paraffin oil droplets meshed in heavy scar tissue gives rise to paraffinomas which may attain several centimeters in diameter Paraffinomas usually occur in clusters about large bronchial branches near the root of the lung In frozen sections fat globules stain bright red with sudan III but only mineral oil fails to turn black in osmic acid

Paraffinomas by pressure on larger bronchi may produce partial obstruction resulting in bronchiectatic dilatation may produce local inflammation and erosion or may be the basis for development of bronchogenic carcinoma Unless a number of sections are taken from different areas of a tumor mass cancer may be overlooked because of the similar appearance of paraffinomas and malignant lesions

[This article and the following one provide added indirect evidence of the possibility of various irritating substances being responsible for bronchogenic carcinoma. The evidence is not accepted generally without many qualifications indicating the need of better proof The recent report of Wynder and Graham (J A M A 143 329 336 May 27 1950) contains data suggesting that excessive tobacco smoking may be an important factor Watson (New York Med 6 15 June 20 1950) offers statistical evidence indicating an absolute increase of cancer of the lung exceeding considerably the proportion of change in the rate of deaths from cancers in other structures such as the stomach prostate and pancreas He likewise is inclined to implicate heavy smoking as a cause on the basis of an analysis of the habits of patients treated in Memorial Hospital New York City —Ed]

Asbestosis and Cancer of Lung *An editor[5] points out that* numerous recent reports tend to indicate a causal relationship between asbestosis and cancer of the lung Incidence of cancer of the lung in persons with asbestosis is excessive (as high as 15 per cent in some reports) since the normal death rate from cancer of the lung among adults examined at autopsy is about 1 per cent Moreover there was a distinct shift in sex distribution of lung cancer in a series of asbestosis cancers recently reported from England Male female sex ratio was 2 4 1 whereas it is 5 1 for cancers of the lung in general This shift indicates that an environmental and evidently occu

(5) J A M A 140 1 19 1 20 Aug 13 1949

pational carcinogen was active in the asbestosis group tending to equalize the incidence of lung cancer for the sexes Recent experimental observations support this interpretation of clinical evidence

Since some 20 000 workers are employed in the asbestos producing industries of this country and Canada and many additional thousands in various asbestos consuming industries more attention by the medical profession to this probable occupational hazard of cancer of the lung is desirable Cytologic examinations of the bronchial secretion may well be included in periodic examination of workers exposed to asbestos dust whenever clinical or roentgen evidence indicates the possibility of a pulmonary cancer Since available evidence shows that occurrence of cancer of the lung is related to pulmonary asbestosis and is not merely a possible sequela of exposure to asbestos dust autopsy with detailed histologic analysis should be done in all fatal cases of asbestosis The anatomic lesions produced by asbestos dust in the lungs at times make it difficult to distinguish by clinical and roentgen diagnostic methods between pneumoconiotic changes and those that might indicate a cancerous growth

Bronchial Carcinoma Practical Method of Early Diagnosis is described by K R Cross T E Corcoran T J Cooper and S N Landis[6] (Veterans Admin Hosp Des Moines Ia) Bronchial aspirations and washings were embedded sectioned and stained and examined microscopically Such preparations amount to minute biopsy specimens (Figs 47 and 48) and show less distortion than is produced when smears are prepared

METHOD —In all cases in which carcinoma of the lung is suspected bronchial aspirations and/or washings are obtained regardless of other findings or procedures The material is placed in Formalin and subsequently centrifuged at 1 000 2 000 rpm for 10-45 minutes After a minimum of four hours fixation the supernatant is decanted and the remaining button treated as any other surgical specimen If four sections are taken from four different levels of the block the likelihood of finding cancerous tissue will be increased

This method was used in 101 specimens from 81 patients Specimens of 2 were suggestive but not diagnostic of 3 strongly suggestive and of 10 diagnostic of cancer No diagnosis of cancer was reported for nine Of this group of 24 pa

(6) A ch Path. 48 491 502 December 1949



Fg 47 (t p) —S ct on f b onch al w h g f eopl t t × 200
Fg 48 (b tom) —B p y p m how g poo ly d ff t d ma
H ma yl d n × 200
(C t y f C os K R t I A h P th 48 491 50 D mbe 1949)

tients carcinoma of the bronchi was subsequently proved at biopsy surgical resection or autopsy or by acceptable clinical criteria

[Th s m thod de erves further investigation in view of the s mplicity which is claimed for it. Cytolog c tudies of bronchial d scharges certainly offer p omi of earlier diagnosis of bronchial ca cinoma —Ed]

Pathology of Subacute Cor Pulmonale in Diffuse Carcinomatosis of Lungs is discussed by A D Morgan[7] (Westminster Hosp London) He describes a case of lymphangitis carcinomatosa of the lungs complicating an undiagnosed gastric carcinoma and giving rise to obliterative endarteritis of the pulmonary vessels with right ventricular hypertrophy

(7) J P th & B t. 61 75 84 J ry 1949

Man 58 was hospitalized with cyanosis, dyspnea and edema and died four days later At age 31 gastroenterostomy had been performed for duodenal ulcer Five years before death emphysema was diagnosed roentgenographically At this time he began to have epigastric pain and during the last three years of his life had much pain and flatulence apparently unrelated to food X ray examination 18 months before death revealed gross emphysema with cor pulmonale A barium meal showed a deformed duodenal cap and pylorospasm suggestive of continued duodenal ulceration

Seven weeks before death another barium meal showed the stoma functioning well after some initial delay, but tumor was not sus



F g 49—T e t on of h rt sh w ng hyp t phy of r ght v t ul mus le Red ed f om × 1 3 (C t y f M rg A D J P th & Ba t 61 5 84 J n ry 1949)

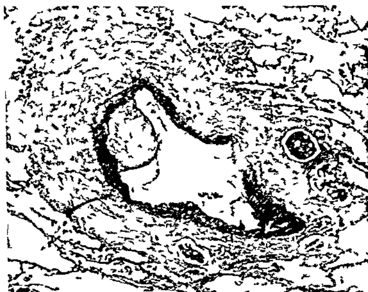
pected A fractional test meal however showed achlorhydria even after histamine One month before admission breathlessness greatly increased and a few days before admission orthopnea and dependent edema developed

He appeared wasted orthopneic and cyanosed with edema of the face elbows hands sacrum and ankles The chest was emphysematous Auscultation revealed a triple rhythm heard most clearly in the epigastrium The liver margin was tender and palpable 4 in below the costal margin

Postmortem examination of the stomach revealed a sclerosing carcinoma of the leather bottle type The heart weighed 370 Gm

the increase being due entirely to hypertrophy of the right ventricle (Fig 49) Microscopic examination of the lungs revealed two main changes (1) Most of the arterioles were completely occluded by a form of obliterative endarteritis (2) The perivascular and peribronchial lymphatics throughout both lungs were distended by plugs of cancer cells (lymphangitis carcinomatosa) (Fig 50)

Study of the literature on diffuse carcinomatosis of the lungs revealed that in three fourths of the cases the primary tumor was a gastric carcinoma seldom diagnosed during life



Fg 50 —P lm nary l h w g f b p oc g w p f m t ma w th p l fib os d H m t yl d os h d d f m × 75 (Court y f M g n, A D J P th & B ct 61 75 84 J y 1949)

Analysis of the histologic reports in 78 published cases showed that there is no clearcut histologic distinction between the group in which spread to the lungs is obviously hematogenous and that in which there is held to be retrograde spread from the hilar lymph nodes (lymphangitis carcinomatosis) One third of the cases of lymphangitis carcinomatosa showed tumor cells in the blood vessels as well as in the perivascular lymphatics frequently associated with diffuse obliterative endarteritis or organized thrombosis

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F g 49 —T ansve e ect of h rt sh w ng hyp t phy f r ght v t cul r m le R d d f m × 1 3 (Co t y f Morg A D J P th & B t 61 5 84 J u y 1949)

pected A fractional test meal however showed achlorhydria even after histamine One month before admission breathlessness greatly increased and a few days before admission orthopnea and dependent edema developed

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All 15 of the patients with adenoma of the bronchus which responded well to endoscopic therapy had the endo bronchial type of tumor Seven were cured and eight became symptom free In all but one of the successfully treated pa tients the tumor was located in the main bronchus or trachea in the one it originated in the right middle lobe bronchus Of patients in whom treatment failed only five had tumors in the main bronchi in the others it was in the lower upper or middle lobe bronchi Thus accessibility of the tumor to bronchoscopic manipulation could be an important factor in determining success or failure In the successfully treated pa tients tumor duration was 3 3 years but for the five main bronchus adenomas not responsive to endoscopic therapy average duration was 21 2 years This long period allows time for extrabronchial extension and favors formation of irrep arable suppurative disease of the lung distal to the tumor conditions requiring surgery for cure Tumors associated with stenosis of the bronchus or having evidence of extrabronchial compression proved not amenable to endoscopic therapy In the successfully treated patients the normal architecture of the bronchus was apparent at the fifth bronchoscopic exami nation

If tumors cannot be eradicated completely and the normal bronchial architecture visualized after a fair trial period sur gery is indicated Recurrent hemoptysis and continued exacer bations of lung suppuration point to the need for surgery Local endobronchial recurrence is evidence of incomplete eradication of a slowly growing tumor and should not suggest malignancy or the need for immediate surgery

[The prognostic significance of bronchial adenoma is till debated There has been increasing evidence that the tumo may be invasive locally and in rare cases it may give ise to metastases in the regional lymph ode As a rule it seems best to resect the lobe or segment of lung conta n ng the neopla m —Ed]

Bronchial Adenoma Herman J Moersch and John R Mc Donald[9] (Mayo Clinic) observed bronchial adenoma in 45 men and 41 women aged 15 67 Cough hemoptysis and pain were the symptoms most frequently complained of In 74 per cent roentgen study showed appreciably significant pulmonary changes Of the 84 patients subjected to bronchoscopy the

(9) J A M A 142 99 104 F b 4 195

Of the 11 cases accompanied by right ventricular hyper trophy 10 showed an obliterative lesion of the pulmonary arterioles in the form of intravascular fibrosis or more recent thrombosis There is thus reason to believe that subacute cor pulmonale is due not to lymphangitis carcinomatosa per se but to occlusion of the pulmonary arterioles The suggestion is made in the light of these findings, that lymphangitis car cinomatosa follows a hematogenous spread of tumor cells to the lungs rather than a retrograde spread from the hilar lymphatics

[The conclusion reached by Morgan seems rational and well sup ported by his evidence Clinically his concept is significant since patients sometimes present symptoms principally of respiratory failure and cor pulmonale which may lead to an erroneous diagnosis of simple fibrosis or some other block between the pulmonary alveoli and capillaries —Ed]

Adenoma of Bronchus Endoscopic Treatment in Selected Cases Max L Som[8] (Mount Sinai Hosp New York City) reviewed 50 endoscopically diagnosed and histologically proved cases of bronchial adenoma This lesion may be dis tinguished from cylindroma a much more invasive variety of mixed tumor which should not be included in this group by the appearance of cells in solid alveolar arrangement with a delicate stroma and the uniformity in size shape and staining character of the cells

Bronchial adenomas may be divided into endobronchial and intramural or extrabronchial types The endobronchial type has a globular shape which accommodates itself to the lumen of the bronchus It presents a smooth polypoid sur face over which the bronchial mucosa is reflected and has a limited attachment to the bronchial wall usually by a pedicle but occasionally is more sessile The other type presents a smooth broad surface endobronchially but extends beyond the boundaries of the bronchus and projects into the peribronchial tissue It replaces bronchial structures and invades adjacent glands In such instances it may cast a dense shadow on the x ray film and occupy a large area of lung parenchyma These tumors probably originate from the bronchial glands or their ducts They are more prevalent among men than women and occur predominantly in the third and fourth decades

(8) J Tho a c S rg 18 462 472 A g t 1949

fibromatosis was present in three of five cases reported in the literature These findings the significance of which is not clear are not of diagnostic aid in differentiating intrathoracic neurofibroma from intrathoracic meningocele but add considerable confusion since mediastinal neurofibroma might be expected as part of a generalized Recklinghausen syndrome



Fig 51—Frontal p j t h w g d m l d d ty pol f l ft th m g 7 m d m e (C t y f By F X t l J Tho S g 18 94 303 J 1949)

Aside from thoracotomy or thoracostomy the only procedure useful in differential diagnosis is intraspinal injection of an opaque medium and *the positioning of the patient so as to fill* if possible the suspected meningocele

The simplest explanation of the production of meningocele would be herniation of the dural envelope of the spinal nerve *through the intervertebral foramen with pressure necrosis of* the vertebral bodies and enlargement of the foramen as the *meningocele enlarges*

adenoma was visualized in 78 and biopsy was positive in all but 3 Apparently adenomas originate in the larger bronchi The best explanation for this localization is that they arise from mucous glands which are more numerous in large bronchi than in smaller ones

In this series 10 per cent of the lesions were of cylindroma type and 90 per cent of carcinoid type Grossly all adenomas tend to polypoid projection into the bronchus but frequently most of the tumor is situated in the bronchial wall and in the adjacent pulmonary tissue Sputum examination is of value in differential diagnosis in bronchogenic carcinoma results are usually positive but they are consistently negative in adenoma Cylindroma usually has a wider base of attachment and therefore presents a more difficult therapeutic problem than adenoma of the carcinoid type In five patients there was definitely proved metastasis and in three others there were probable metastases which were not proved microscopically

Of the 36 patients treated bronchoscopically 19 are living 6 have had recurrence with subsequent operation 6 are dead and the follow up is incomplete for 5 Of 51 treated by surgery exploration only was performed in 3 40 are well and 8 are dead Bronchoscopic treatment is recommended for patients with a pedunculated adenoma situated so that it can be removed readily for elderly patients and for those with lesions situated close to the carina so that pneumonectomy would have to be performed After bronchoscopic treatment repeated examinations with the bronchoscope are necessary because of the likelihood of recurrence Surgery is advisable for all other patients and those with evidence of recurrence

Intrathoracic Meningocele Francis X Byron (Los Angeles) Emery E Alling (Battle Creek Mich) and Paul C Samson[1] (Oakland Calif) report three cases of intrathoracic meningocele and emphasize that this lesion must be differentiated from the more frequent intrathoracic neurofibroma With either lesion the chest x ray may disclose a uniformly opaque well defined rounded or lobulated intrathoracic mass (Fig 51) and rib changes intervertebral foraminal enlargement or vertebral body destruction (Fig 52)

Superficial neurofibromas and cafe au lait spots were observed in one patient another had cafe au lait spots Neuro

(1) J Tho c S g 18 294 303 J n 1949

Pulmonary Adenomatosis of Man Review of Literature and Report of Nine Cases Lawrence L Swan (Army Inst of Pathology) proposes that the term pulmonary adenomatosis be reserved for pulmonary tumors which show alveolar cellular proliferation of tall columnar mucus producing type absence of an intrinsic tumor of the bronchial tree and absence of primary adenocarcinoma of any other part of the body Average age in the nine cases reported was 47 2 years there were eight males and one female In eight cases symptoms were of 4 15 months duration and in one there were no symptoms the lesion being discovered by routine chest x ray History of exposure to pulmonary irritants was not significant Signs and symptoms in order of frequency were productive cough fever dyspnea weakness weight loss thoracic pain fatigue cyanosis night sweats pleural effusion and clubbing of the fingers Eight patients have died The survivor who was treated by lobectomy was alive at the time of this report Histologically the cases fulfilled all the criteria for pulmonary adenomatosis Metastases were limited to parenchymal lymphatic channels in one lung and to parenchymal lymphatic channels and hilar lymph nodes in another There was widespread metastasis in only one case Confirmation of metastases was not possible in one case in which pneumonectomy was done but autopsy refused

In the 27 acceptable cases in the literature since 1941 the patients ages varied from 17 to 79 There were 12 males and 15 females Evidence of invasion or metastasis was present in 55 6 per cent These data are to be contrasted with the fact that bronchogenic carcinoma occurs far more frequently in males than in females Furthermore they support the statement that most alveolar cell tumors are malignant

When death has resulted from pulmonary adenomatosis the pleural space is usually partially or completely obliterated by fibrous adhesions The pleural cavity may contain fluid in varying amounts and the lungs are voluminous and tend to retain their contours when the chest is opened The visceral and parietal pleurae may be studded with gray to grayish pink nodules The gross distribution of these tumors may be of miliary nodular type diffuse or a combination of these The

( ) A h P th 47 517 544 J 1949

Once intrathoracic meningocele is diagnosed the question of advisability of operation arises Among the previously reported cases the two patients on whom excision of the sac was performed died of empyema and meningitis neither had received chemotherapy In both cases difficulty was encountered in closing the defect In one of the authors cases a satisfactory closure while difficult was attained It is recommended

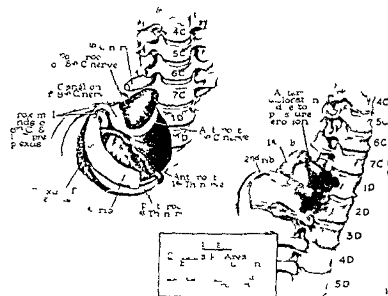


Fig 52—D w g dem t t g lat n f m n go l to 6 t d d rbs nd to l w tr nk of b h l pl E t t f b a d l de struct n is sh wn t ght (Co rt y f By n F \ rt l J Th c S g 18 294 303 J e 1949)

that a generous portion of the neck of the sac be saved so that a plicated closure can be carried out A second patient died of shock probably the result of bleeding encountered during surgery In the third patient operation revealed a meningocele in the apex of the right chest but it was not treated because it was asymptomatic and in a protected place If the sacs are relatively small operation is probably not justified unless serial chest x rays reveal progressive enlargement to the point of progressive respiratory embarrassment

Pulmonary Manifestations of Scleroderma Anatomic Physiologic Correlation David M Spain and Albert G Thomas[3] (Columbia Univ) report a case of scleroderma in which the clinical features were almost entirely related to pulmonary changes

Man 65 had had shortness of breath for 10 years It became progressively worse and was accompanied by ankle edema He was told he had heart disease and was treated unsuccessfully with large doses of digitalis for several years About four years before admission a cough productive of a variable amount of sputum was noted Since that time he had noted changes in the skin and joints Dyspnea cough expectoration and weakness had become progressively severe

In the hospital skin biopsy led to a diagnosis of scleroderma The vital capacity was 1 750 cc and residual air 921 cc compared with normal values of 4 140 and 1 335 cc respectively Arterial oxygen saturation at rest was 91 1 per cent and after exercise 81 per cent The right ventricular blood pressure was 71/ mm Hg compared with a normal of 28/0 4 The arterial blood pressure was 118/67 mm Hg During the hospital stay weakness increased and dyspnea became so severe that continuous administration of oxygen was required He died 106 days after admission

At autopsy the right lung weighed 900 Gm and the left lung 770 Gm In both the pleura was diffusely granular thickened and opaque *The upper lobes of both lungs and the middle lobe of the* right were almost completely consolidated and airless On the cut surface there were many thin walled cystlike spaces ranging in size from 2 mm to 1 cm Microscopic examination of lung sections (Fig 53) revealed many varying sized cystic spaces often lined by cuboid epithelium Alveolar septa were diffusely thickened with fibrous tissue and in places infiltrated by inflammatory cells Bronchioles were dilated and in many of the smaller ones the muscular coat was partially replaced by fibrous tissue Pulmonary arterioles had thick walls and narrow lumens

In scleroderma involvement of skin diaphragm fibrous retraction of the pleura and diffuse peribronchiolar fibrosis interfere with the function of getting air in and out of the lungs The most striking changes in the case reported were related to impairment of the respiratory function by pro

(3) A I t. M d 32 15 161 J y 1950

histologic picture is essentially the same in the two forms Variations in pattern may range from simple investment of alveoli by a single layer of cuboidal or cylindric cells to complicated arrangements resulting from extensive intra alveolar proliferation of the cells with rupture of alveolar walls and coalescence of spaces

The appearance of the lesions of pulmonary adenomatosis or alveolar cell tumor of the human lung are similar to those in jagziekte a disease of the lungs of sheep and lesions in horses mules guinea pigs and cats It is possible that an identical pulmonary reaction takes place in these widely different species A review of the causes of adenomatosis in these species may shed light on the condition in man As yet no etiologic factor has proved to be specific for the condition in man but the disease apparently is not infectious

Origin of the epithelium like tumors in adenomatosis is undetermined The recent literature has shown a significant trend toward acceptance of the theory of an alveolar epithelial origin Swan supports the view that it is an extrabronchial neoplasm with cancerous potentialities since though it may appear histologically benign it may kill by local growth or by metastases

[The important practical implication of this report is that the diseased lobe or lung should be resected if the adenomatosis is so localized and a proper diagnosis can be made Diagnosis is difficult and in the presence of such chronic diffuse lesions direct biopsy of the lung may be necessary —Ed]

ciated cardiac changes of pericardial fibrosis focal myocardial fibrosis with thickening of the myocardial arterioles subendocardial fibrosis and hypertrophy with dilatation of the right ventricular myocardium combined to produce myocardial anoxia and pulmonary hypertension

Essential Brown Induration of Lungs (Idiopathic Pulmonary Hemosiderosis) N G B McLetchie and Grant Colpitts[4] (Regina Sask) state that this condition is not familial but has been encountered in children aged a few months to 16 years It is characterized by periodic attacks of tachycardia pyrexia pallor fatigue cyanosis increasing dyspnea signs of congestive cardiac failure severe anemia and hemoptysis Lung findings are usually more conspicuous by x ray than clinically and consist of a diffuse bilateral infiltration of coarse mottling against a general background of increased density Between attacks the subject may remain well but usually there is chronic ill health The condition ends fatally

At autopsy the only conspicuous abnormality is in the lungs The lungs are uniformly consolidated and have a firm rubbery consistency the cut surface is a uniform brown red without evidence of inflammatory processes A copious blood stained frothy fluid may be extruded from the cut surface on pressure Microscopically there are alveolar thickening due to capillary dilatation thickening of capillary and alveolar basement membranes generalized interstitial edema and generalized increase of reticulin and collagenous fibrils The elastica in the lung is grossly deficient and almost completely absent in the alveolar walls and septa The lung consolidation is due to filling of the alveoli with red blood cells and macrophages laden with hemosiderin Almost all the changes can be considered secondary to anoxemia

Although the essential nature of the disease is unknown lung inelasticity due to hypoplasia of the elastica or a vasomotor abnormality of the lesser circulation may be of primary importance

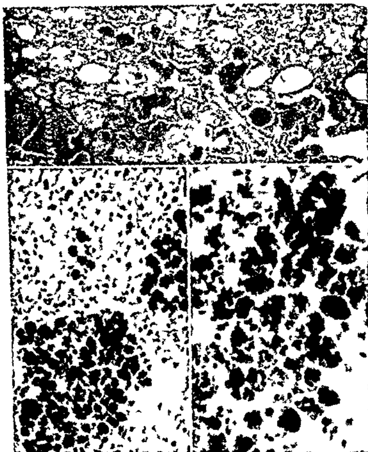
Hemosiderosis of Lung Due to Mitral Disease Report of Six Cases Simulating Pneumoconiosis According to Eugene P Pendergrass Edwin L Lame and Herman W Ostrum[5] (Univ of Pennsylvania) mitral valve disease may be accom

(4) Canad M A J 61 1 9 133 Aug t 1949
(5) Am J Roe tg 1 61 443 456 Ap 1 1949



Fig 53—Photomicrograph of lung Hematoxylin and eosin ×20 (Courtesy of Spain D M and Thomas A C Ann. Int. Med. 3 132 161 J   y 1950)

nounced thickening of alveolar walls narrowing of arterioles and thickening of their walls These changes interfered with exchange of gas over the alveolar interface as illustrated by a low oxygen content of arterial blood after exercise Asso



F g 56 (t p) —H stop thol g c d ta l f l g f m p ti t how g d 6b l g l l mps f m phag nt g h m de n most y tra l l Th k d pt d b o pas c g l n re een R d c d f m × 3

F g 57 (b ttom l ft) —R d ed f m × 400

F g 58 (bott m ght) —R l d f × 950

(Cou te y f P derg as E. P t al Am J Roe tg n l 61 443 456 Ap l 1949)

from numerous others that may produce a finely nodular x ray density in the chest Helpful confirmatory evidence i a mitral configuration of the heart and a history of rheumatic valvular disease

panied by deposition of hemosiderin in the lungs so that x rays reveal a fine nodulation (Figs 54 and 55) resembling pneumoconiosis or miliary tuberculosis This condition is rare only 17 cases studied at autopsy being collected from the world literature In the series reported four cases were studied at autopsy two patients are still living

Of the four cases studied at autopsy all showed chronic passive congestion some of which was severe In two there was hemosiderosis and in the others siderofibrosis All the



Fig 54 (left) —X ray of patient dying of rheumatic mitral heart disease at t p y diag wa p lm a y s de of b os
Fig 55 (right) —Nodules o e tg nog m m a e up t 3 mm n d m t r (Courtesy of P nd rg s E 1 *et al* Am J Roentg 61 443 456 Ap 1949)

microscopic sections contained nodular aggregates that could be identified grossly as areas of hemosiderin deposition (Figs 56 58) By the Prussian blue test diagnosis was confirmed The aggregates of iron pigment varied from 1 to 3 mm in diameter Their size distribution and shape govern the degree of x ray visualization

As evidenced by the diagnosis in two living patients this condition occurs in those with mitral valve disease living comfortably without clinical evidence of lung congestion It is conjectured that these persons have hemosiderosis with in active chronic passive congestion

For diagnostic purposes the lesion must be differentiated

aid of antibiotic drugs seven patients are still alive The sur vivors ages range from 2 to 14½ years

Chest x rays may disclose extensive pulmonary changes which can be divided into two stages In the first there is evidence of bronchial plugging without much infection and the picture of obstructive emphysema with poor air exchange may be recognized The second stage shows infection with



F g 60 —Sect on f b on h f m l ft l g b w g m tarl f ep th l m. (Co te y f D Ley L B D s. f Ch t 17 151 156 F bru ry 19 0)

increased hilar shadows and prominence of vascular mark ings Bronchiectasis is usually present but use of lipiodol[*] is not warranted for confirmation In long standing pulmo nary disease the apexes and bases are equally involved but there is no evidence of pleural reaction Irregularly emphysem atous lungs prominent hilar shadows and bronchovascular markings extensive peribronchial pneumonia areas of atelec tasis bronchiectasis and bronchiectatic abscesses may be noted but are not specific though they should suggest the diagnosis

Pulmonary Disease, Associated with Cystic Fibrosis of Pancreas, is discussed by Lloyd B Dickey[6] (Stanford Univ) who reports experience with 10 patients In any child with a chronic respiratory infection especially if it extends from the tip of the nose to the alveoli with sputum and negative tuberculin this disease should be suspected at once Sex distribution was about equal four had symptoms from birth whereas two did not have symptoms until age 14 months The initial symptom in five was cough and in five it was the character of the stool Cough and respiratory symptoms developed in the latter group in 14 months to 5 years A history of a sibling dying previously with a clinically similar disease was found in three cases Typical stools with increased fat content were noted in seven When the tests were carried out four showed no trypsin activity in the duodenal contents and four showed minimal activity



Fig 59 —C t s fa of l ft l g of f nt wh d d t g 7 m th h w ng ch s p p t b o ch t b n h ect pper l b d p ed e l g m t of pe b ch l d (C t y f D key L B D s f Ch st 17 151 156 F b y 1950)

There was decided evidence of paranasal sinusitis in four three had pronounced heavy chronic nasal discharge and two had postnasal pus Otitis media occurred in three including one without evidence of sinusitis The sputum of seven contained Staphylococcus aureus coagulase positive and in one hemolytic streptococci were found but in two bronchial secretions contained no pathogenic organisms Physical examination disclosed malnutrition in all but one and chest involvement in all x ray studies showed pronounced lung involvement in all but one Death occurred in one patient at age 7 months and in another at age 27 months Both showed fibrocystic disease of the pancreas and extensive pulmonary disease (Figs 59 and 60) consisting of bronchitis pulmonary abscess bronchiectasis and bronchopneumonia With the

(6) D f Ch t 17 151 156 F bru y 1950

generalized disease of unknown etiology occurring in an acute or chronic form In the acute variety which occurs in infancy and early childhood there is progressive infiltration of the skin bone lymph nodes and viscera leading to early death The chronic variety occurring in older patients may be present in the complete form with pituitary bone and lung dis



F g 61 (l ft) —C) t f t ght f m below ld f t
F g 6 (ght) —(l d t l t both l g
(C t y f P k son T B t M J 1 10 9 1030 J 31 1949)

ease or in the incomplete form in which one or a combination of these systems is involved In the chronic form lung fibrosis and cyst formation may be the sole manifestations or there may be association of pituitary disorders with honeycomb lungs

Radiologic Morphology of Fatty Embolism of Lung was followed serially by Georges Voluter[8] (Univ of Geneva) The patient was a man aged 25 who had a comminuted fracture of the left femur and died three days after onset of coma

(8) A t ad 1 31 403 430 1949

Early and vigorous treatment should be instituted for the pancreatic deficiency and should include large amounts of vitamin A If pulmonary symptoms are striking oxygen should be administered and tenacious mucus secretions removed by mechanical suction Penicillin aerosol should be instituted but in small infants the intramuscular route may be used If penicillin resistant organisms appear streptomycin or aureomycin may be useful Adequate dosage should be continued until the respiratory tract is clear of disease and to some extent prophylactically during remission Local treatment sometimes surgery may be needed for sinusitis Avoidance of exposure to infection should be rigid at all times and all prophylactic measures must be used against such diseases as measles and pertussis

Eosinophilic Xanthomatous Granuloma with Honeycomb Lungs Thomas Parkinson[7] (St Bartholomew s Hosp London) points out that eosinophilic granuloma Hand Schuller Christian disease and Letterer Siwe disease are but phases of the same disorder and to avoid confusion recommends that the terminology of Thannhauser eosinophilic xanthomatous granuloma be used He reports the following case

Man 56 was hospitalized in September 1948 complaining of increasing dyspnea on exertion during the preceding six years Because of the x ray finding of diffuse pulmonary shadows at the time of onset of symptoms he had been treated in a sanatorium In 1944 the right femur had been fractured X rays showed a cyst at the fracture site The fracture healed well in four months but nine months before admission pain recurred at this site There was onset of polydipsia and polyuria seven months before admission which could be partially controlled by a proprietary pituitary snuff Physical examination disclosed a few rhonchi and some thickening of the right femur over the site of the old fracture An x ray of the femur (Fig 61) showed a cystic area and there was generalized reticulation associated with miliary mottling of both lung fields in the chest x ray (Fig 62) Tomography confirmed the presence of mall cystic areas in the lung A biopsy of the right femoral cyst was thought typical of eosinophilic granuloma of bone Diabetes insipidus was controlled by pitressin® tannate and pain in the leg was completely relieved by a course of deep x ray therapy to the femur Deep x ray therapy to the pituitary fossa and lungs did not change the appearance of the chest x ray or improve the symptoms

Parkinson suggests that this condition be regarded as a

(7) Brit M J 1 10 9 1030 Jun 11 1949

generalized disease of unknown etiology occurring in an acute or chronic form In the acute variety which occurs in infancy and early childhood there is progressive infiltration of the skin bone lymph nodes and viscera leading to early death The chronic variety occurring in older patients may be present in the complete form with pituitary bone and lung dis



Fg 61 (l ft) —Cy t f t ght f m b low ld f t
Fg 62 (ght) —C l d t l t bo b l g
(C t y f P k T B t M J 1 1029 1030 J 11 1949)

ease or in the incomplete form in which one or a combination of these systems is involved In the chronic form lung fibrosis and cyst formation may be the sole manifestations or there may be association of pituitary disorders with honeycomb lungs

Radiologic Morphology of Fatty Embolism of Lung was followed serially by Georges Voluter[8] (Univ of Geneva) The patient was a man aged 25 who had a comminuted fracture of the left femur and died three days after onset of coma

(8) A ta d 1 31 403 430 1949



F 63 —L ft ppe and m ddl p r h l r Not d lat t f l ft n t cle. S co d ph (24 ho s ft t f ma) of f tty bcl m f l g The an almo t l ly t l t t c e d t a p t (w t l p t g) Phase f confl ence of ac nar d t and te t t l f F th fi t t m t h t sh d w e d p p lly t the ght (C t y f Vol te G *Act* d l 31 403 430 1949)

The three following morphologic phases were distinguished

1 A roentgenogram made 26 minutes after onset of coma showed an agglomerated miliary stage of two types images due to fatty and medullary filling of vessels of the pulmonary circulation and embolic elements (follicular stellate foci) in the general circulation The heart shadow was unchanged

2 In a roentgenogram made 24 hours after onset of coma the large agglomerated foci had disappeared and there was confluence of acinar and interstitial foci in both circulations The heart shadow was increased for the first time—more on the left than on the right—and the amplitude of contractions was decidedly decreased The homogeneous shadows (milky aspects) in the peripheral parenchyma hilar region and even in the hilar projection itself must be due to atelectatic exudative phenomena caused by circulatory disturbances (edema) and by aeration disturbances (Fig 63) Because of its morphologic elements this phase could be called the atelectatic exudative and miliary stage

3 Three days after onset of coma there was a purely granular stage which was hard to demonstrate There was an astonishing rarefaction of the pathologic picture but examination under magnification revealed over the entire pulmonary area a crop of small stellate foci with extremely low radioabsorption The small size of the heart was striking

The physician must be alert and must use all available precision methods to discover the slightest trace of a miliary constellation which although only visible in the upper and subparietal areas may give a clue to an intense process disseminated over the entire pulmonary surface

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DISEASES OF THE PLEURA

Defensive Mechanisms in Mediastinum, with Special Reference to Mechanics of Pleural Absorption were investigated by G H Cooray[8] (Univ College Hosp Med School London) Particulate matter introduced into the pleural cavity of animals was found to pass through definite zones in the me

(8) J P th & B ct. 61 551 567 O t b 1949

diastinal pleura These points of exit known as Kampmeier s foci are guarded by collections of macrophages which lie im mediately below the pleural mesothelium (Fig 64) The phagocytes form an efficient protective mechanism because they ingest India ink bacteria red blood cells oil globules silica and colloidal dyes such as trypan blue very quickly Although the pleura actively participates in absorption these barriers prevent dissemination of irritants in the mediastinum



Fig 64—Inj t d [illegible] e d of t d c pl sh w ng l K mpm r foc w th l tw k H h m t yl d d t m × 60 (C t y f Coo y G H J Path & B t 61 551 567 O t b 1949)

and by the blood stream Clinical experience with mediastinitis supports these observations Structures morphologically iden tical with Kampmeier s foci in animals have been demon strated in human mediastinal pleura The presence of these structures may partly explain why the mediastinum is so re sistant to infection from the pleural cavity

Activity of Kampmeier s foci is intimately connected with the direction of movement of intrapleural fluids which in turn depends on respiratory movements The motive force is pro vided mainly by contractions of the diaphragm During dia phragmatic descent on inspiration strong suction causes the intrapleural contents to be drawn toward the diaphragm from

the potential space between lung and chest wall Expiration is not sufficient to drive fluid back to its original position It escapes into the region between the lungs and the retrocardiac mediastinal pleura where there are collections of phagocytic cells Diaphragmatic paralysis abolishes movement toward the absorptive zones and particulate matter remains in the pleural cavity

Absorption is preceded by attachment of particles to the mesothelium over the Kampmeier s foci Penetration of particles occurs only in these foci which serve as natural pathways and as a means of exit for pleural fluids In passage through the pleura particles pass both between the mesothelial cells and through their living cytoplasm Transmission is effected by respiration in the early stages and by carriage within phagocytes in the later stages of absorption The mesothelium lining Kampmeier s foci is distinctly different from the rest of the pleural mesothelium The cells are of smaller size and there is a consequent increase in the total amount of intercellular space Mucin occurs in these cells and probably assists in the attachment of particles to the phagocytic systems When trapped in this manner bacteria are more easily attacked by the macrophages

Reactions of the foci after entry of particles depend on their nature but the end result—localization of the irritant and prevention of its spread—is similar in all instances The macrophages proliferate after phagocytic activity and coalescence of adjacent foci results India ink is ultimately completely encapsulated by mature fibrous tissue Bacterial suspensions incite violent inflammatory reactions and polymorphonuclear exudate but the final result is similar Intrapleural injection of red cell suspensions is followed by formation of hemosiderin exclusively within the ingesting phagocytes in these foci Absence of free particles in the mediastinal tissues is demonstrable evidence of the efficiency with which these foci act as barriers in the pleura Intensity of phagocytosis is enhanced by deep breathing or dyspnea

In experimental mediastinitis it was observed that India ink or bacterial particles introduced directly into the mediastinum follow a characteristic course moving away from the midline toward the pleura This movement serves as a safety device causing irritants to leave vital thoracic structures so

that they can be efficiently dealt with by phagocytes of the Kampmeier s foci There is also a caudal spread toward the base of the mediastinum where irritants reach the retrocar diac pleura with consequent exposure to foci in this location These two modes of spread are mainly instrumental in pre venting gross damage to the lungs and pleura Formation of localized abscesses is another protective device which pre vents dissemination in mediastinal tissues Kampmeier s foci because of their strategic position in the mediastinum act as barriers to the spread of infection either to the pleural cavity or from the mediastinal tissues They constitute the mediasti num s first line of defense

[This is an unusually informative study The infrequency of medi astinal invasion by bacteria and other particulate matter from the pleura always impresses the clinician but the mechanisms of defense have been poorly understood

It is necessary to distinguish between mediastinitis and mediastinal pleurisy clinically The latter occurs relatively often and represents in flammation of the pleura covering the mediastinal space the tissues within the space seldom participate in the inflammation —Ed]

Pleural Shock Andrew Morland[9] (Univ College Hosp London) reports five cases of serious accidents in paracen tesis of which one was fatal These cases represent an inci dence of about 1 in 10 000 punctures of the pleura All oc curred during aspiration of fluid a procedure invariably pre ceded by local anesthesia There was some degree of infection in all and in one case there was irritation of the pleura Air embolism can probably be excluded in all cases The evidence suggests that disturbance of the heart from reduction of intrathoracic pressure is the most likely cause of the sudden loss of consciousness Such accidents are more likely to hap pen when the pleura is thickened and inelastic and it is there fore important to avoid very low pressures during aspiration or replacement of fluid

Air embolism is the most likely explanation of the rare serious or fatal accident during pleural puncture Sudden death without signs or symptoms of cerebral embolism does not necessarily mean shock since with a patient in the hori zontal position air may occlude the coronary vessels Pas sage of air through the chest wall is not essential for produc tion of air embolism for as in the cases described by Morland it may occur during aspiration of fluid

(9) L cet 2 10 1 1023 Dec 3 1949

When lung tissue is indurated by chronic inflammation the veins are held open and cannot contract when mechanically injured The needle may make a communication between airway and vein and deep respiration may suck sufficient air into the vessel to cause embolism Other causes of syncope during paracentesis include status lymphaticus and the psychic effect of needle puncture

Mechanism of Pleural and Ascitic Effusions with Suggested Method for Indirect Estimation of Portal Venous Pressure, is discussed by A H James[1] (St Mary s Hosp London) Antecubital venous pressure and effusion fluid pressure were measured simultaneously in 17 patients with pleural *effusions and in 24 with ascites Congestive failure constric*

MEAN FLUID PROTEIN LEVEL (GM /100 ML.) IN DIFFERENT DISEASES

	P v		A	
	Album	Cl b l	Alt m	Gl b l
Heart failure	1 3	0 8	1 8	1 3
Constrictive pericarditis	1 9	1 2	2.2	2 3
Carcinoma	2 9	1 3	2 4	1 2
Tuberculosis	3 1	2 2	3 1	2 1
Nephrosis		..	0	0.2
Cirrhosis	..	...	0 5	0 7

tive pericarditis carcinomatosis tuberculosis and cirrhosis were the commonest causes of effusions The albumin and globulin content of plasma and of effusion fluid were determined in each patient and the colloid osmotic pressures calculated (table)

Venous pressure always exceeded pleural pressure in patients with pleural effusions The difference between the two was approximately equal to the difference between the colloid osmotic pressures of plasma and fluid Venous pressure ex*ceeded ascitic pressure in most of the patients with ascites* due to causes other than cirrhosis The difference between the two was proportional to the difference between the colloid osmotic pressures of plasma and fluid This proportionality was not observed in patients with ascites due to cirrhosis In seven of nine of these patients ascitic pressure exceeded venous pressure and the difference between the colloid osmotic pressures was large owing to the low protein content of ascitic fluid It is suggested that portal obstruction accounts for the

(1) Cl S 8 291 314 D mbe 1949

different behavior of ascites due to cirrhosis and that the magnitude of the deviation provides a measure of the portal pressure If cirrhosis of the liver is excluded because in this condition portal obstruction intervenes, the findings are in general agreement with Starling s theory that a proportionality exists between the colloid osmotic and hydrostatic forces

The albumin content of effusion fluid was proportional to that of plasma but the globulin contents were not related except in tuberculous pleurisy Effusion fluids caused by tuberculosis or carcinoma contained more protein than those caused by congestive failure The correlation of plasma and effusion fluid albumin levels is most easily explained by assuming that some of the capillaries in contact with the effusion are permeable to albumin so that it enters effusion fluid largely by simple diffusion Globulin probably only enters effusions when capillary permeability is markedly increased by inflammation The general supposition that inflammatory diseases cause effusion of fluid with large amounts of protein in contrast to congestive failure cirrhosis and nephrosis is confirmed

Hypoproteinemia is usually found in patients with effusions being more severe in those with ascites particularly if caused by cirrhosis

Pulsus Paradoxus and Pleurisy W Eric Gibb reports two cases in which pulsus paradoxus occurred in association with massive pleural effusion It is well known that idiopathic pericarditis and pleurisy may coexist and that when of tuberculous etiology either may be fibrinous or exudative But it is also well to recognize that pulsus paradoxus can occur in the presence of a large pleural effusion alone and therefore such inspiratory waning of the pulse does not necessarily indicate pericardial effusion Whereas a pericardial effusion which gives rise to pulsus paradoxus should give other signs of its presence but frequently results only in moderate dyspnea a pleural effusion of sufficient size to give rise to pulsus paradoxus is also accompanied by marked dyspnea and distress Pulsus paradoxus in a case of pleural effusion is an indication for removal of 20 30 oz fluid immediately

Pulsus paradoxus in pericardial effusion and mediastino pericarditis is coincident with severe interference with venous

(2) B t J T b c 43 1 6 J ary 1949

filling of the right side of the heart whereas its presence in deep inspiratory breathing in normal subjects is associated with pooling of blood within the pulmonary circulation and therefore a lessened venous return to the left side of the heart In gross intrathoracic disease including massive effusions and after pneumonectomy blood flow to the left auricle is likewise decreased and therefore output from the left side of the heart lessened

Study of Coagulation Mechanism of Pleural Blood in Hemopneumothorax is presented by Stuart W Cosgriff[3] (Columbia Univ) In a patient with hemopneumothorax the pleural blood failed to clot on removal from the chest but its hemoglobin content hematocrit and plasma specific gravity were comparable to that of circulating intravascular blood The essential constituents for coagulation prothrombin thrombin and fibrinogen were completely absent from the pleural blood specimen Calcium was present in normal amounts When the hemothorax plasma was recalcified for prothrombin determination it failed to clot It was impossible to demonstrate any form of anticoagulant activity in the pleural blood though incoagulability was confirmed on several occasions

Since the essential factors for coagulation were absent it was concluded that coagulation had occurred before thoracentesis Apparently coagulation of blood proceeds within the pleural cavity in the usual fashion and the so called incoagulable hemothorax fluid was really serum in which some of the formed elements of the blood were suspended

[The accumulation and defibrination of extravasated blood in the pleura has been observed frequently in clinical practice The fibrin sometimes forms into a ball particularly in the presence of pneumothorax and this may move about in the pleural space after serum has been ab orbed Eventually the fibrin ball becomes fixed and is absorbed or organized —Ed]

Relation of Idiopathic Pleurisy and Pleural Effusion to Tuberculosis K S Maclean[4] (Cambridge Univ) noted that in 17 of 107 Royal Navy personnel with pleural effusion but in only 2 of 120 with dry pleurisy tuberculosis subsequently developed The difference in subsequent incidence of tuberculosis in the two groups is highly significant and indicates that

(3) Am J Med 8 57 61 J y 1950
(4) G y Hosp R p 97 133 184 1948

tuberculosis is much more likely to follow pleural effusion than idiopathic dry pleurisy

Upper respiratory infection was twice as common before dry pleurisy as before effusion Fever disappeared in less than three weeks in 87 3 per cent of patients with dry pleurisy but persisted longer in 79 2 per cent of those with effusion Fluid was present more than six weeks in 87 4 per cent of those with effusion whereas in 89 7 per cent of those with dry pleurisy friction rub disappeared in less than six weeks Sedimentation rate was more likely to be elevated in patients with effusion but leukocytosis was rare in both conditions From x ray evidence it is apparent that dry pleurisy has much in common with bronchitis or bronchopneumonia and occurs more frequently in the higher age groups than does pleural effusion

Tuberculosis is more likely to follow when the effusion is large its duration long and fever sustained and is even more likely when the patient is between 20 and 30 The commonest tuberculous complication of effusion is an infiltrative lesion at the common situation for postprimary tuberculosis the subapical areas of the upper lobes Results agree with the accepted view that the likelihood of sequelae decreases with time

In differential diagnosis of pleural effusion transudates may be distinguished from exudates in that the former have a specific gravity under 1015 a low protein content and no clot formation They are frequently associated with cardiac or renal disease Effusions secondary to malignant disease or pyogenic lung infections are often difficult to differentiate from those due to tuberculosis Malignancy is the commonest cause of effusion in patients over 40 and may be differentiated by thoracoscopy pleural biopsy x ray examination of the lung fields after removal of fluid by aspiration or detection of malignant cells in the pleural fluid or sputum Aid in diagnosis of pneumo or streptococcic effusion may be derived from the rapid response of fever to chemotherapy high leukocyte count elevated respiratory rate in the absence of severe pleuritic pain absorption of effusion within three to four weeks and the finding of a predominately polymorphonuclear fluid A history of a pleuritic incident within the previous six months is strong evidence that tuberculosis is the responsible agent Patients in whom a pleural friction rub of dry pleurisy

persists for more than two or three weeks are more likely to develop tuberculosis than those in whom signs and symptoms clear rapidly In general every case of idiopathic pleural effusion must be considered tuberculous until proved otherwise but the converse is true for dry pleurisy

Direct inhalation into the lungs must be the usual route of infection in pulmonary tuberculosis For production of tuberculous effusion tubercle bacilli or tuberculoprotein must come *into contact with a hypersensitive pleural membrane* The latter appears to develop some months after the primary complex Such an effusion almost always occurs on the same side as the complex but the exact route by which the bacilli reach the pleural membrane after primary infection has not been settled Should organisms come into contact with a nonhypersensitive pleura dry pleurisy may result Once the pleura has developed hypersensitivity effusion may occur at any stage of the disease

Tuberculous pleural effusion commonly follows Mantoux conversion when this occurs after adolescence but is extremely rare before age 15 although most persons have become Mantoux positive at this age The explanation for this may lie in the fact that the initial tuberculous infection is greater after adolescence because at that age larger droplets containing a greater number of bacilli are able to pass the lung defenses and reach the terminal bronchi It is postulated that size of the droplets which reach the terminal bronchioles in children is very much smaller than in adults possibly because of the more efficient working of the ciliated epithelium and consequently the number of virulent organisms is correspondingly less Since adults tend to receive a larger initial *dose of infection the primary complex remains active longer* and hypersensitivity develops while the pleura is still subjected to the action of tubercle bacilli with the result that fluid is produced

Pleural fluid complicates obvious pulmonary tuberculosis much less commonly than might be expected and is probably due *to formation of tubercles on the pleural membrane or rupture* of a small tuberculous cavity into the pleural space This relative rarity is probably due to the tendency for bacilli to remain localized to the lesion and to obliteration of the pleural space in the vicinity of the lesion The infrequent association

of miliary tuberculosis with effusion may be due to the rapidity with which the infection spreads allowing little time for hypersensitivity to develop

Reinfection following tuberculous effusion is by an endogenous source such as the initial focus the obliterated basal pleural space and adjacent subpleural areas of the lower lobes In these situations fibrous reaction and concentration of tubercle bacilli is greatest

Infrapulmonary Pleural Effusion Simulating Elevation of Diaphragm Emil Rothstein and Francis B Landis[5] (Veterans Admin Hosp Wood Wis) observed 12 cases of this condition 6 in association with pulmonary tuberculosis 1 with bronchogenic carcinoma 1 with heart disease 1 with postpneumonic empyema 1 with metastatic hypernephroma and 2 of unknown etiology Because of the concave shape of the lung base the fluid assumes a convexity superiorly which resembles an elevated diaphragm in the standard posteroanterior x ray The convex upper border of infrapulmonary effusions has never been adequately explained but it may be due to fortuitously situated pleural adhesions or encapsulation of the fluid In some of the present cases encapsulation was proved by failure of the fluid to shift with changes of position but in nine patients the fluid shifted and in several lateral decubitus films revealed a free pleural space Factors altering lung retractility may be important in localizing the fluid but in five patients the lower lung was normal by x ray The basic cause of this configuration is obscure

Diagnosis of infrapulmonary effusion may be aided by careful study of consecutive x rays which reveal the sudden appearance of unexplained elevation of the diaphragm in a patient whose earlier films had no such change Development of minimal blunting of the costophrenic angle is an additional help in diagnosis When the left side of the chest is involved the stomach or colon may contain gas and by their position give a clue to the true level of the diaphragm As a diagnostic procedure 2 drachms citrocarbonate may be used to outline the stomach

Fluoroscopic examination may reveal the exact nature of the condition Diaphragmatic motion is usually well transmitted to the overlying fluid and its presence may rule out

(5) Am J Med 8 46 52 J ary 1950

phrenic paralysis and subphrenic abscess In most cases a definite shift of the fluid is noted in different postures In the supine position the two leaves of the diaphragm become equal and the involved side diffusely more opaque than previously owing to a shift of the fluid along the posterior chest wall X ray studies should be made in the dorsal recumbent and lateral decubitus positions Pneumoperitoneum may be helpful in revealing the true position of the diaphragm particularly on the right side Thoracentesis provides positive proof of an effusion but may be unsuccessful if the fluid is pocketed or so deeply situated as to be inaccessible

Differential diagnosis includes elevation of the diaphragm from various causes subphrenic abscesses hepatomegaly diaphragmatic hernia lung tumors intrathoracic cysts and atelectasis

Empyema as Complication of Chronic Pulmonary Tuberculosis In 1 874 consecutive autopsies of chronic pulmonary tuberculosis reviewed by Oscar Auerbach[6] (Halloran Veterans Admin Hosp Staten Island N Y) there were *311* cases of empyema an incidence of 16 per cent In the vast majority the empyema cavity was located in the lateral aspect of the chest It usually extended from the inferior aspect of the upper to the base of the lower lobe In all regions the boundary of the empyema cavity was the fused visceral and parietal layers of the pleura

Artificial pneumothorax was present in 252 (81 per cent) of the 311 cases of empyema whereas in 59 (19 per cent) there was no such antecedent treatment This substantiates the general opinion that empyema is chiefly a complication of artificial pneumothorax Bronchopleural fistulas were present in 153 cases (49 1 per cent) In many other cases of empyema there was a definite episode which pointed to the presence of a fistula during the patient s life These episodes included marked shifts of the mediastinum to the opposite side rapid appearance of highly positive pleural pressures on the affected side expectoration of methylene blue instilled into the pleural cavity and shortness of breath and pain on the side of involvement Auerbach believes that the cause of the empyema in each instance was a bronchopleural fistula although in many the fistulas were healed at the time of autopsy

(6) Am. R T be c. 59 601 618 J 1949

There was no evidence at autopsy of rupture of an adhesion band in artificial pneumothorax (due to stretching) with subsequent development of empyema In no case could it be proved that the pleural space had become infected from without Evolution of a clear serous effusion into an empyema almost always results from bronchopleural fistula not discovered clinically

In 180 cases (72 per cent) artificial pneumothorax was begun within the first seven months of onset of the disease Empyema is generally an early complication of this therapy but may appear at any time as long as the collapse is maintained in the presence of an open cavity In none of the cases in the present series was there evidence of rupture of an empyema into the lung parenchyma Empyema necessitatis was a complication in 32 cases (9 7 per cent) In all but four it was associated with artificial pneumothorax

The Blood *and* Blood-Forming Organs

WILLIAM B CASTLE M.D S M (Hon.) Yale
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PART III

THE BLOOD AND BLOOD-FORMING ORGANS

ADVANCES IN KNOWLEDGE CONCERNING DISEASES OF THE BLOOD 1940-50

During the past decade many new observations and some concepts concerning diseases of the blood and blood forming organs were doubtless influenced by the war For example the practical need for large amounts of blood and blood substitutes for the armed forces led to the development of blood banks the fractionation of plasma with its various useful by products and studies of the survival of red cells in health and disease Renewal of interest in the chemotherapy of leukemias and lymphomas is also an offshoot of research in the leukopenic effect of toxic war gases These illustrate the hastened fruition of prewar inquiries the roots of which lay just beneath the surface The majority have been covered in the YEAR BOOKS of the decade How much the disturbance of the soil nourishing the deep lying seeds of the significant research of the future may have cost the world we shall never know but may gravely suspect

GENERAL PHYSIOLOGY

In the work of Moore and his associates is found experimental confirmation in man of the physiologist s belief in the basic control of erythropoiesis by the oxygen content of the arterial blood Breathing of high concentrations of oxygen had depressant effects on reticulocyte hemoglobin and red cell production in various types of hemolytic anemia Return to breathing of room air at once resulted in increased bone marrow activity From the work of Young and his colleagues who used the mechanical fragility method of Shen in studies of the survival of dog red cells tagged with radioactive iron it would appear that mechanical destruction in the moving circulation is the factor

limiting the life of successive generations of normal red cells This has been determined at from 100 to 120 days by improved methods of estimating survival differential agglutination of compatible but heterologous transfused red cells tagging with radioactive iron or persistence of circulating hemoglobin containing heavy nitrogen (N^1) after the feeding of glycine containing that isotope

In other studies London Shemin and Rittenberg found that N^1 containing glycine became incorporated into the red cell hemoglobin of nucleated duck red cells and of human sickle cells in vitro Although they could not correlate this effect with the presence of young red cells (reticulocytes) Finch and his colleagues did so in similar experiments employing radioactive iron They and other workers also showed that vitamin B_1 and pteroylglutamic acid directly promote the synthesis of hemoglobin by the nutritionally deficient erythroid cells of the bone marrow of patients with pernicious anemia To this specialized location for the synthesis of hemoglobin in the body the iron is transported bound to a beta globulin of the plasma after being absorbed in ferrous form and according to Granick temporarily combined in ferric form in the intestinal wall with the peculiar protein apoferritin

The classic method of estimating the rate of red cell destruction has been the determination of the output of fecal stercobilin presumably a quantitative derivative of hemoglobin However by the use of N^{15} containing glycine it now appears from the studies of London and his associates that at least 15 per cent of the stercobilin output in the normal individual is not derived from the breakdown of circulating hemoglobin In pernicious anemia this excess may amount to as much as 50 per cent It is thus possible that as was long ago suggested by Whipple bile pigment production may short circuit in part the insertion of hemoglobin into the finished red cell The work of Whipple and MacKenzie has clearly demonstrated that the normal spleen is a filter with capacity to distinguish and selectively to retain spheroidal as opposed to normally discoid red cells or according to Bjorkmann starch grains of 5 as opposed to 3 microns in diameter

From cross circulation experiments in leukopenic cats J S Lawrence has shown that leukocytes (in contrast to red cells) live only a few hours in the circulation being replaced on the

average about three times a day According to Jersild granulocytes younger than metamyelocytes are rarely phagocytic The endocrine system has been linked to leukocytosis by the demonstration of Cress and others that leukocytosis fails to appear after anoxia or convulsions in rats whose adrenal medullas have been removed Leukocytosis is seen however in the intact animal or in man after the administration of pituitary adrenocorticotrophic hormone Even in the absence of the adrenal medulla the injection of foreign protein causes leukocytosis probably because of liberation of the products of the inflammatory response that has been studied by Menkin The work of Dougherty and of White although not confirmed in all aspects postulates the lysis of lymphocytes in the nodes and in the circulation as a result of adrenocortical stimulation Clinically the eosinopenia resulting from the administration of pituitary adrenocorticotrophic hormone or of cortisone is even more striking in the normal subject It has been postulated that the lympholysis which occurs is a part of the alarm reaction of Selye and is beneficial to the organism by releasing antibody globulin from the lymphocyte The experimental work of Ehrich Kass Fagraeus and others has presented strong evidence that the responsibility for production of antibodies resides not as formerly supposed directly with the reticuloendothelial cells but rather with the lymphocytes or plasma cells of the lymphoid apparatus

A great deal of research has been reported in the field of blood coagulation rather to the confusion of the innocent bystander Out of the welter of terminology—different names for the same thing same name for different things—has emerged important new knowledge Tocantins did a service to clinical thinking in his article on hemostasis and its disturbances due to extravascular vascular and intravascular defects Lawrence using cross circulated irradiated cats concluded that platelets in circulation live from three to five days The Zuckers have shown us the platelets at work mechanically plugging the injured arterioles and apparently giving off vasoconstrictor substances in the process Jacques s introduction of silicone coated glassware has made it possible to handle blood in the laboratory almost as if it were still in the blood vessels and to separate by centrifugation various components without the deleterious influence of the wetted glass surface

The classic two stage concept of blood coagulation of Mora

witz became fundamentally modified by the clinical observations of Owren in 1944 In the study of a woman with a bleeding di athesis he discovered that the delayed prothrombin time of the blood could be returned to normal by the addition of traces of prothrombin free normal plasma containing what he eventually called factor V This accelerator of the conversion of prothrom bin to thrombin is either the same substance or if not possesses

INACTIVE PROTHROMBIN
PROTHROMBIN
PLASMA AC GLOBULIN [1]
SERUM AC GLOBULIN
CALCIUM
PLATELET FACTOR 1
PLATELETS [2]
? PLATELETS [3]
THROMBOPLASTINOGEN
THROMBOPLASTIN
THROMBIN
FIBRINOGEN — FIBRIN
(PLATELET FACTOR 2)
(CALCIUM)

F g 65 —Blo d coagul t on uto t lyt c ct Se g s Q ck M! to e (Sl ghtly mod fied f m W J Ha n gt s figu)

an action similar to that of components of fresh plasma variously called labile factor accelerator globulin or serum pro-thrombin conversion accelerator by others As a result the present concept of blood coagulation may be represented by the diagram shown in Figure 65

Against this background of increased knowledge of the physiology of blood have come important advances in pathology diagnosis and treatment of disorders of the red and white cells and of hemorrhagic diseases due to platelet or plasma abnor malities These will now be considered in this order

Red Cell Disorders

The decade opened with important discoveries The previous year Levine and Stetson had called attention to the role of the fetus in causing isoimmunization of the mother in pregnancy Wiener and Peters then presented examples of hemolytic trans fusion reactions resulting from sensitization to previous trans fusions with red cells containing the Rh factor In conjunction these discoveries led to understanding of the immunization re

actions responsible for erythroblastosis fetalis—antibody formation in the Rh negative mother bearing an Rh positive child with passage of antibodies into the fetal circulation via the placenta. Today we know that no female who requires a transfusion is Rh negative and has not yet passed the menopause should be given Rh positive blood in any form unless her life is in immediate jeopardy.

The working out of the complex genetic background of the allelomorphic genes of the Rh Hr system derives from the brilliant contributions of Fisher and Race. Discovery by Race and by Wiener of the so called incomplete or blocking antibodies explained the frequent failure of maternal serum to agglutinate the red cells of the erythroblastotic infant in the conventional saline dilution system. This obstacle was surmounted by working with suspensions of Rh positive cells in undiluted serum *(Diamond) or in bovine or human albumin solution.* Coombs, Mourant and Race devised a nonspecific but sensitive method of testing for the presence of antibodies adsorbed on the surface of washed red cells suspended in saline. For this purpose they developed an antiserum in rabbits against human serum or human serum globulin. This technic was useful not only in the study of erythroblastosis but even more so in the recognition of adsorbed proteins on the surface of the red cells of patients with so called acquired hemolytic jaundice. Unfortunately no method of prevention has been successful but development of the exchange or exsanguination transfusion of Rh negative blood has been of therapeutic benefit to the severely affected infant. Diamond recently reported the surprising observation that for this purpose the blood of female donors is especially useful.

Acute blood loss from wounds was a major problem of the war. The anticoagulant acid citrate dextrose solution greatly improved the viability of the red cells when subsequently transfused. Group O blood, not always a safe preparation for emergency transfusions because of a high agglutinating titer of the plasma against heterologous *recipients' cells, was rendered safe* by the addition of Witebsky's A and B substances derived from gastric tissue. Where, as in obstetric hospitals, the risk of reactions or of immunization against the Rh factor is to be avoided at all costs, universally safe blood is, in addition, required to be Rh negative. Such improvements in technic together with the use of packed red cells (Mollison, Alt) in severe anemias in

which the added plasma is a useless diluent highlight progress in the last few years Today the hazard of transmission of serum hepatitis especially by pooled plasma can be avoided by ultra violet irradiation or treatment with nitrogen mustard a method that can be applied even to whole blood

Much knowledge has been gained concerning the mecha nisms of increased red cell destruction The occasional acute hemolytic anemia due to exposure to chemicals such as arsine naphthalene quinine acetanilid and sulfanilamide was shown by Emerson and Ham to result from injury to the red cells by oxi dant derivatives of such drugs The oxidants tested were active even in vitro in increasing the mechanical fragility of red cells In severe burns the direct action of heat on the red cells caused similar increases in mechanical fragility

Demonstration of the short survival time of the red cells of congenital hemolytic jaundice in normal subjects by Dacie and Mollison and of sickle cell disease by Singer Moore and their respective associates clearly indicated a defective red cell per haps because of its demonstrable increased mechanical fragility Owren has demonstrated that the so called familial or anemic crises in congenital hemolytic jaundice are in reality due to temporary inhibition of bone marrow activity rather than to increased red cell destruction In congenital hemolytic jaun dice the increased mechanical fragility of the red cells results largely from changes in the cells occurring during sequestration in the spleen In sickle cell disease it is a direct physical result of the sickling process Sickling when the abnormal red cell is deprived of oxygen or exposed to reducing agents is ascribed by Pauling to an abnormal type of hemoglobin Harris has just demonstrated that even solutions of this hemoglobin exhibit orientation and alinement of the molecules when deoxygenated

In both thalassemia (Cooley s anemia) in which the causes of the abnormal red cell formation and destruction remain ob- scure and sickle cell disease a major and a minor form of the disorder have been recognized Genetic studies by Neel indi cate that the severity of the pathologic manifestation in red cells of both diseases depends on whether the affected individual is hetero or homozygous for the special hereditary trait In paroxysmal nocturnal hemoglobinuria Ham has demonstrated an abnormality of the red cell that causes its lysis in native or foreign human plasma when slightly acidified The physiologic

increase in acidity of the blood especially in stagnant areas during sleep is presumably the cause of the nocturnally aug mented hemolysis

Abnormal plasma is now recognized as responsible for sev eral types of acquired hemolytic anemia The avidity of such plasma components for the red cells largely thwarted attempts at their demonstration in plasma until the positive reaction to the Coombs test shown to be characteristic of such patients by Boorman Evans and others led to more critical studies of plasma and tissues Dacie has recently described the presence in rare instances of a hemolysin active against all types of red cells when the serum is slightly acidified

It is well known that in many cases of acquired hemolytic anemia spontaneous agglutination of the red cells is observed This is frequently due to a cold agglutinin In many instances however as shown by Gardner there is an agglutinin demon strable at body temperature with augmentation when the serum is acidified Extending the concepts of Ham and Castle to the study of hemolysis in mismatched transfusion reactions occur ring without demonstrable hemolysins but with incompatible agglutinins Shen has shown in experimental animals that ag glutination alone results in sequestration of the red cells in the liver and other organs with subsequent ischemia and release of lytic substances from the tissues In patients with acquired hemolytic jaundice exhibiting a positive reaction to the Coombs test and autoagglutination of the red cells both phenomena are more marked in the blood in the splenic pulp than in blood in the periphery Wagley and others demonstrated further that the splenic pulp in such patients has the property of conferring a positive Coombs reaction on normal red cells Splenectomy in acquired hemolytic jaundice although not as in congenital hemolytic jaundice an almost certain cure may be beneficial This has been well demonstrated by Dameshek Splenectomy probably is effective because it removes an important source of abnormal agglutinin with avidity for the red cell and also elimi nates an organ capable of selective retention of agglutinated red cells with subsequent lysis Gardner has found that adreno corticotrophic hormone (ACTH) may temporarily halt a hemo lytic crisis and so make splenectomy feasible

During the decade a brilliant chapter of new knowledge con cerning nutritional macrocytic anemias was written with the aid

which the added plasma is a useless diluent highlight progress in the last few years Today the hazard of transmission of serum hepatitis especially by pooled plasma can be avoided by ultra violet irradiation or treatment with nitrogen mustard a method that can be applied even to whole blood

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ability for vitamin B_{12} may not also help to condition the development of pernicious anemia The therapeutic activity of vitamin B_{12} is phenomenal in that 0 001 mg is apparently roughly equivalent to 1 U S P unit of liver extract when injected However vitamin B_{12} does no more (and also probably no less) as a therapeutic agent than does liver extract Its chief promise is its anticipated cheapness as a by product of antibiotic manufacture and its freedom from species sensitivity an effect sometimes observed with liver extracts

The studies of Bomford and Rhoads of so called refractory macrocytic anemias—disorders that came into prominence with the successful treatment of pernicious anemia and its relatives—constitute a classic description The patients display variability of bone marrow morphology from aplasia to hyperplasia and immaturity of the numerous cells In half the patients significant histories of exposure to cyclic compounds were obtained The histologic findings present a suggestive analogy to those of Hunter and Mallory in patients with chronic exposure to benzol In a few patients frank leukemia developed To the list of chemicals occasionally toxic to all elements of the bone marrow the decade added new substances such as atabrine* and tridione* Few advances in knowledge concerning other types of anemia beyond increased information about the appearance of the bone marrow as a result of the more frequent use of needle or trephine biopsy have been made For needle biopsy the iliac crest or vertebral spinous process is to be preferred to the sternum in the main for psychologic reasons Until recently studies of the effects of irradiation though actively pursued by many workers appear to have turned up little that is novel However Jacobson has just made the important observation that shielding of the spleen during irradiation of animals in some way promotes subsequent bone marrow recovery even though the spleen is soon removed

Shaefer has produced polycythemia in dogs by resection of the carotid and aortic depressor nerves The resulting neurogenic hypertension presumably causes a generalized peripheral vasospasm and hence stagnant anoxia of the bone marrow Renewed emphasis on the relation between myelogenous leukemia and polycythemia vera has been laid by several reports of patients whose disease progressed terminally to frank leukemia sometimes acute in type Because radiation is a slow acting leu

especially of microbiologic research In 1945 folic acid a growth factor essential for certain lactobacilli was made available in synthetic form by Angier and his associates for clinical trial Later its formula was disclosed as pteroylglutamic acid This yellow compound unexpectedly was found by Spies and later by others to be at least initially highly effective in all varieties of nutritional macrocytic anemia including pernicious anemia and sprue It was first thought to be the antipernicious anemia principle of liver but this belief was soon discarded because of its virtual absence in purified liver extracts With the aid of microbiology and of chromatographic separation of substances with a red color noted to be associated with clinical activity crystalline vitamin B_{12} was isolated from liver in 1948 almost simultaneously by the American Folkers and his associates and the British workers headed by Smith To Randolph West who with Dakin was a pioneer and later a persistent seeker of this goal went the honor of first demonstrating its clinical efficacy in pernicious anemia Subsequent work indicates that although folic acid fails in many instances to prevent or to arrest the development of spinal cord lesions in pernicious anemia vitamin B_1 seems to be fully as satisfactory in this respect as is purified liver extract However in certain cases of nutritional macrocytic anemia usually associated with pregnancy and with grossly defective diets vitamin B_1 like purified liver extract is devoid of activity In such patients orally administered crude liver extract or folic acid is gratifyingly effective Very recent clinical observations by Luhby and experimental work by May appear to indicate that the megaloblastic anemia of infancy is the result of a combined partial deficiency of folic acid and ascorbic acid

From the work of Berk Hall Bethell and others it appears that vitamin B_1 is probably both the so called extrinsic factor and the antipernicious anemia principle of liver The role of the intrinsic factor of gastric juice thus appears to be specifically to promote the absorption of vitamin B_1 from the alimentary tract In the broad tapeworm anemia of Finland according to Bonsdorff the worm when situated in the upper part of the alimentary tract is apparently able to inhibit the action of the small residual amount of the intrinsic factor characteristic of these patients Watson s recent studies with aureomycin raise the question of whether intestinal bacteria with demonstrable

duced with extracts of normal organs or with nucleic acid Thus it appears to resemble the occasional intense leukemoid reaction occurring in man from necrosis of tumors or other tissues The diagnosis of the type cell in blood samples bone marrow or lymph node biopsies continues to offer some indication of a better prognosis when well differentiated cells in patients in the older age groups are observed On the other hand the fluid evolutionary trends fast or slow to more malignant forms in the transitional histology of follicular lymphoma to Hodgkin s disease reticulum cell sarcoma or lymphosarcoma and lymphatic leukemia have been emphasized by Custer and Bernhard

The etiology of leukemia is a mystery its palliation a daily task its cure a fervent hope of many physicians It has become clear that the therapeutic effects of radioactive phosphorus (P^{3}) resemble closely those of x rays useful prolongation of life especially in chronic myelogenous leukemia little of value in acute forms and lymphomas It is thus not a significant addition to our therapeutic armamentarium albeit on occasion its less frequent dosage schedule is a convenience

The renaissance of interest in chemotherapy stems from the development of the so called nitrogen mustard war gases Of these methyl bis (β chloroethyl) amine hydrochloride (HN) is the most effective but must be given intravenously A recent modification (melamine) is given by mouth and is said not to cause the nausea and vomiting usually associated with the use of HN_2 From the experience of Rhoads Dameshek Jacobson Wintrobe and others it appears that these compounds are particularly useful in Hodgkin s disease especially when x ray can no longer be tolerated or when there is diffuse visceral involvement or signs of intoxication The remissions induced appear quickly but are usually shorter than those caused by x ray Urethane therapy introduced in 1946 by Paterson was found to be particularly effective in chronic myelogenous leukemia Rundles and Moloney believe it also to be useful for multiple myeloma characterized by a fairly mature type of plasma cell The early hopes aroused by stilbamidine in this disease have not been fulfilled In acute leukemia of children Farber and his associates as well as others have observed partial or complete remissions in occasional cases of several weeks or even months duration from the use of analogues of pteroylglutamic (folic) acid Several workers have reported short remissions in acute leu

kemogenic agent it is highly unlikely that spray x ray or P^{32} administration shortly preceding this development was a causative factor More probable is the supposition that the polycythemia was secondary to a latent and primary chronic myelogenous leukemia as may sometimes be the case in multiple myeloma

White Cell Diseases

Infectious lymphocytosis first described by Smith in 1941 has subsequently been reported by others as well in small epidemics among children and young adults The pronounced leukocytosis mostly of fully mature lymphocytes with little cytoplasm and a negative heterophil test chiefly distinguish it from infectious mononucleosis In the latter disease spontaneous rupture of the spleen has been reported several times The well recognized clinical appearance of jaundice in some patients was found by Peterson to be the expression of disturbed liver function occurring without visible jaundice in 20 of 40 patients A convenient rapid slide agglutination test with sheep cells has been devised by Moloney Hargraves has described the artificial production of the characteristic L E cell originally observed in bone marrow smears of patients with lupus erythematosus by incubation of plasma of these patients with bone marrow cells from individuals with unrelated conditions

In the prior decade the devastating effect of sepsis secondary to agranulocytosis itself due to drug sensitivity was clearly recognized Consequently when all methods of stimulating leukocyte production were found to be unreliable the discovery of the sulfonamides provided a direct attack on the infection This procedure introduced by Dameshek was almost at once improved upon by the use of penicillin which lacked the leukotoxic properties observed with the sulfonamides in other patients Such a regime permitted spontaneous recovery to occur under its protection Several cases of cyclic leukopenia of uncertain origin have been reported as well as the neutropenia ascribed by Wiseman and Doan to splenic hyperfunction

Furth s expert review of experimental leukemia in 1946 provided a valuable documentation although many physicians are skeptical of the analogy to the human diseases The myeloid metaplasia of the bone marrow described *by Heinle and by* Miller as produced in experimental animals given injections of extracts of the urine of patients with leukemia can also be in

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In the prior decade the devastating effect of sepsis secondary to agranulocytosis itself due to drug sensitivity was clearly recognized Consequently when all methods of stimulating leukocyte production were found to be unreliable the discovery of the sulfonamides provided a direct attack on the infection This procedure introduced by Dameshek was almost at once improved upon by the use of penicillin which lacked the leukotoxic properties observed with the sulfonamides in other patients Such a regime permitted spontaneous recovery to occur under its protection Several cases of cyclic leukopenia of uncertain origin have been reported as well as the neutropenia ascribed by Wiseman and Doan to splenic hyperfunction

Furth s expert review of experimental leukemia in 1946 provided a valuable documentation although many physicians are skeptical of the analogy to the human diseases The myeloid metaplasia of the bone marrow described by Heinle and by Miller as produced in experimental animals given injections of extracts of the urine of patients with leukemia can also be in

Measurable variations in platelet adhesiveness have been proposed by Wiener and by Moolten to explain lack of correlation between clinical bleeding and platelet levels in various types of thrombocytopenia Cryoglobulin as a cause of purpura of distal portions of the extremities has been ascribed by Lerner and Watson to local cooling with increase in blood viscosity or protein precipitation in the capillaries The use of antiheparin compounds (protamine and toluidine blue) in controlling bleeding as introduced by Allen is difficult to evaluate In a clinical study of the effects of splenectomy Robson clearly differentiated the prompt and nonspecific effects of the operation in shortening bleeding time and in increasing capillary resistance from the later rise of platelets which is possibly more specifically related to removal of the organ

According to Quick and Stefanini prothrombin A is removed from plasma by precipitation with tricalcium phosphate and is decreased by vitamin K deficiency (biliary obstruction or steatorrhea) liver disease and dicumarol® administration Prothrombin B is lacking in rare instances as a hereditary anomaly Labile factor disappears from plasma on standing has the various synonyms already referred to and is an even more rare congenital defect causing as do other types of prothrombin deficiency intermittent hemorrhagic phenomena Davidson and his associates recommend vitamin K_1 oxide as more efficient than simpler naphthoquinones in shortening the prothrombin time after dicumarol® overdosage

In hereditary hemophilia the earlier studies of Patek Taylor and their associates demonstrated a euglobulin in normal plasma capable of correcting the coagulation defect for several hours Its practical use in the form of fresh blood or plasma transfusions or of plasma fraction I of Cohn has been found by Frommeyer Epstein and Taylor to result in some patients in the evolution of a refractory state characterized by presence of an anticoagulant antibody in the patient s plasma Quick believes that the defect in hemophilia is one of plasma thromboplastinogen This being so even the normal platelet disintegration at the site of injury under the influence of thrombin does not result in normal blood coagulation

In patients other than hemophiliacs anticoagulant substances of a different character have occasionally been reported Heparin is said to have appeared in the blood of certain patients fol

kemia from adrenocorticotrophic hormone therapy after which the patient usually becomes refractory to this material

Because these various compounds exert profound effects on normal hemopoiesis and other body cell systems doubtless by inhibition of enzyme systems characteristic of many types of normal cells it is not surprising that their effects are relatively nonspecific in the treatment of disease and are accompanied by injury of normal tissues There can be no doubt however that there are specific biochemical differences between the neoplastic and the normal cell Their discovery will lead to far better control perhaps even cure of these conditions

Hemorrhagic Diseases

The question of whether the hemorrhages in thrombocytopenic purpura are due to abnormal capillaries as observed by MacFarlane or to defective mechanical plugging by platelets as noted by Zucker is not answered with finality Perhaps the normal platelet is in effect a potential partner in a durable capillary wall as is the mortar in a wall of bricks Quick and his associates have clearly demonstrated that thrombocytopenia leads to delay in the formation of a firm clot by failing to activate plasma thromboplastinogen The resulting lack of quantitative formation of prothrombin and therefrom of thrombin fails to provide the coarse fibrin strands essential to firm clot retraction and vessel sealing With thrombocytopenia the trivial amount of surface coagulation taken as the end point in the usual clotting time determination may be almost within normal time limits However it may be accompanied by little evidence of a significant continuing production of thrombin For this among other reasons Quick s prothrombin consumption (i e conversion to thrombin) test is a useful measure of the completeness of coagulation

In a study of the thrombocytopenic purpura not infrequently occurring with sedormid* (allyl isopropyl acetyl carbamide) therapy Ackroyd demonstrated local purpura with patch test and agglutination of the platelets by this and related open chain ureide compounds in plasma samples from sensitized individuals Since the first reports by Moschowitz and by Baehr and his associates several cases of an acute febrile usually fatal purpura associated with diffuse platelet thromboses of arterioles and capillaries have been described The etiology remains obscure.

GENERAL CONSIDERATIONS

The articles selected for this section cover some general aspects of normal and pathologic physiology of the blood and blood forming organs. The first five articles are concerned with basic processes in hemoglobin and red cell formation —Ed.

Role of Oxygen in Regulation of Erythropoiesis Depression of Rate of Delivery of New Red Cells to Blood by High Concentrations of Inspired Oxygen. Oxygen tension of the environment is regarded as one of the principal regulators of rate of erythropoiesis This concept is based largely on the fact that stimulation of red cell formation regularly occurs at high altitudes or under conditions of decreased oxygen tension Evidence that the converse is true that high tensions of oxygen can decrease erythrocyte formation is more fragmentary A few experiments have demonstrated that animals become anemic within a few weeks when placed in atmospheres containing 60 per cent or more of oxygen at normal barometric pressure but definite evidence that such occurs in man has been obtained only in patients with sickle cell anemia John C Tinsley Jr Carl V Moore Reubenia Dubach Virginia Minnich and Moises Grinstein[1] (Washington Univ) attempted to demonstrate that the phenomenon was a general one and not limited to sickle cell anemia

Oxygen was administered continuously for 8-14 days through a meter face mask to two patients with sickle cell anemia one with congenital hemolytic anemia four with untreated pernicious anemia and two men with late syphilis in whom red cell equilibrium was normal

With oxygen concentrations of 50 per cent or more in the inspired air the following evidences of erythroid depression were regularly observed In chronic hemolytic anemia during the oxygen period there were dramatic decrease in number of reticulocytes fall in red cell count of approximately 1 000 000 cells and a slower rate of radioactive iron utilization for hemoglobin synthesis After oxygen was discontinued decided reticulocytosis developed red cell count returned rapidly to control level and utilization of radioactive iron was accelerated In patients with pernicious anemia injection of

(1) J Clin I vestigation 8 1544 1564 November 1949

lowing irradiation or the administration of HN In contrast to other hemorrhagic disorders the characteristic tendency to bleeding in the joints of hemophiliacs and the lack of correlation between coagulation time and bleeding manifestations have perhaps at last received an explanation Thus the work of Tocantins and of Soulier appears to indicate a relative deficiency of tissue thromboplastin in hemophilia Soulier found no such difference as exists normally between the prothrombin time of venous and of capillary blood presumably because in the hemophiliac the capillary blood is not significantly contaminated with tissue thromboplastin as a result of the needle puncture

In rare congenital instances such as that reported by Corbett the blood fails entirely to clot because fibrinogen is almost completely or even entirely absent from the blood Adequate coagulation can temporarily be achieved with transfusions or better intravenous administration of fraction I of Cohn containing fibrinogen Following surgical or hemorrhagic shock or particularly premature separation of the placenta (Wiener) severe bleeding may occur and samples of the patient s blood are found to coagulate briefly and then again to liquefy This is due to the presence of fibrinolysin recently studied by MacFarlane and by Tagnon among others The phenomenon of fibrinolysis is presumably the result of activation of an enzyme precursor by products of tissue autolysis

—WILLIAM B CASTLE

oxygen o curred without any alteration in pH of arterial plasma and in the absence of toxic manifestations The mechanism by which oxygen tension of environment affects erythropoiesis is not known The most commonly held theory is that one of the factors which controls red cell production is oxygen tension in marrow itself Since chronic hypoxia is associated with secondary polycythemia it is assumed that the resultant low oxygen tension in marrow stimulates erythrocytogenesis

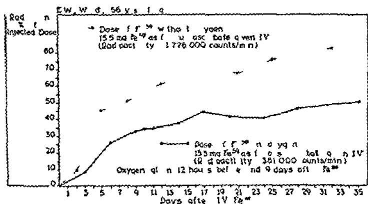


Fig 67—Ut l f Fe⁵⁹ f h m glob n y th by m l t du g t l pe od a d d g h l t f 70 pe t g (C t y f T a l y J C J m f J Cl l t g t 28 1544 1564 N ml 1949)

Conversely if erythroid tissue is exposed to an increased oxygen tension rate of red cell formation would be expected to decrease The authors results are compatible with this idea

Hemin Synthesis in Spleen Homogenates It has been demonstrated that the alpha carbon atom of glycine is incorporated in the hemin and globin moieties of the hemoglobin molecule when glycine labeled with C^{14} in the methylene carbon atom is fed to rats Hemin synthesis in vitro has also been demonstrated in several instances Since there exists histologic evidence of extramedullary hemopoietic activity in the spleen Kurt I Altman and Kurt Salomon[2] (Univ of Ro hester) thought it of interest to test with biochemical methods the possibility of hemin synthesis from labeled glycine in spleen homogenates

METHOD —A spleen homogenate from three rabbit spleens was

( ) Sc 3 117 118 F b 3 1950

therapeutic doses of liver extract or of vitamin B_1 while high concentrations of oxygen were being given caused a submaximal reticulocyte response (Fig 66) During the post oxygen period a second reticulocyte crisis larger than the first occurred in each instance In subjects with normal blood formation radioactive iron injected intravenously during oxygen administration was delivered to peripheral blood as newly formed hemoglobin at a rate distinctly less than nor

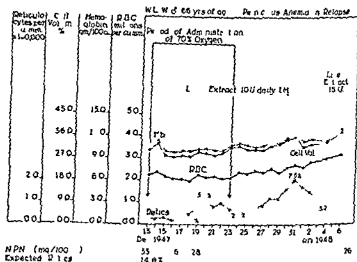


Fig 66 —Eff t f 0 pe c nt oxygen on th pe t r pen to l r tt t (Co t y f T n l) J C Jr et a J Cl n In t g ti 8 2544 2564 N m be 1949)

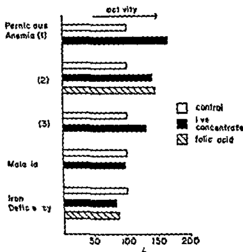
mal (Fig 67) There was also a small but definite decrease in reticulocytes which corrected itself after oxygen was removed Several weeks after these observations utilization of radioactive iron was again studied so that each subject could serve as his own control Curves obtained in the second study fell within the normal range There remained no doubt therefore that utilization of iron was depressed during oxygen administration

These data indicate that oxygen breathed in concentrations of 50 per cent or more depresses rate of erythropoiesis in normal human subjects in patients with chronic hemolytic anemias and in patients with pernicious anemia This effect of

in the red cell stroma capable of removing iron from the serum and (2) the synthesis of heme

Similar incubation studies were conducted on bone marrow aspirations Uptake of radioiron by normoblasts was much greater than that in reticulocytes Again radioactive heme could be demonstrated after incubation of radioiron with marrow cells

Radioiron can be used as an indicator of altered hemopoiesis (Fig 68) Suspensions of marrow from patients with



F g 68 —M w b t Eff t f f) ac d and l M ow ell obtained by t nal j t on f m pat ent w th t ted per io m how d cr se ds pt k f 66 44 and 8 pe t f dd e f 0 00001 t f) 5 g f l d (Court y f Wal b R J *et al* Sci 110 396-398 O 14 1949)

untreated pernicious anemia repeatedly showed an acceleration of the rate of iron uptake after addition of liver or folic acid compared with control studies This did not occur in conditions other than those characterized by specific deficiencies of the substances used These observations indicate that liver and folic acid act directly on immature erythrocytes of marrow cells in untreated pernicious anemia

[However recently Horrigan and Vilter have found that vitamin B_{12}, but not folic acid is active when injected *locally* in maturing the megaloblasts of the bone marrow of the iliac crest in pernicious anemia —Ed]

prepared glycine labeled with C^{14} in the methylene carbon atom was added and the homogenates were then incubated for appropriate periods After addition of crystalline hemin as carrier either hemin or protoporphyrin IX dimethyl ester was isolated and determination of C^{14} activity was carried out with an ionization chamber apparatu

Results indicated that hemin synthesis can be carried out by rabbit spleen homogenates utilizing the methylene carbon atom of glycine as a precursor

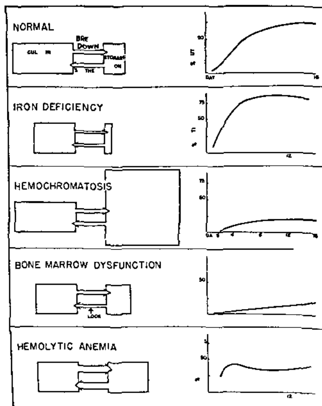
Iron Metabolism Heme Synthesis in Vitro by Immature Erythrocytes Studies with radioiron have indicated that there is no exchange of iron between the mature erythrocyte and surrounding plasma R J Walsh E D Thomas S K Chow R G Fluharty and C A Finch[3] present data however which indicate that reticulocytes assimilate iron and synthesize heme in vitro and that this uptake of radioiron may be used as an indicator of the rate of hemoglobin synthesis In vitro studies using Fe^{59} and Fe^{5} were performed in rocking boats at 37 C in a gas mixture of 95 per cent oxygen and 5 per cent carbon dioxide

Whereas blood containing less than 1 per cent reticulocytes took up no measurable quantity of radioiron uptake was demonstrated repeatedly in blood with a high reticulocyte count It was shown that radioactivity was localized in the immature cells by correlating reticulocyte count and radio activity in various fractions of this blood Blood was studied from individuals with various types of anemia including iron deficiency acquired hemolytic sickle cell and pernicious ane mia Uptake of iron in all instances was attributable to pres ence of reticulocytes It further appeared that at least in per nicious anemia rate of uptake was also related to the type of reticulocyte present The early reticulocytes after liver therapy contained more reticular material and picked up more radio activity

To determine whether the uptake of iron indicated hemo globin formation red cells were fractionated after incubation with radioiron The greatest activity in the reticulocyte por tion was found in stroma of hemolyzed cells However signifi cant amounts of radioiron were also demonstrated in recrys tallized heme from these cells These observations indicate that the physiologic process of assimilation of iron by the de veloping red cell is (1) the attachment of iron to acceptors

(3) Sc e e 110 396 398 Oct. 14 1949

Among eight patients with viral bacterial and protozoal in fections utilization curves were extremely depressed in those severely ill One patient with sickle cell anemia one with congenital hemolytic anemia and three with acquired hemo



Fg 69 (C t y f F h C A t l Blood 4 905 9 6 A g t 1949)

lytic anemia showed a rapid initial utilization rate and max imal values were *obtained in three to five days However* total amount of iron in the circulation was low Of three pa tients with pernicious anemia two were given radioiron before liver therapy was effective and utilization was retarded In the third however radioiron administered several days after

Iron Metabolism Utilization of Intravenous Radioactive Iron Iron is rigidly conserved by the body and no attention need be directed to its excretion in absence of blood loss This conservation emphasizes the importance of the metabolic cycle in the body in which iron is used again and again for hemo globin formation Clement A Finch John G Gibson II Wendell C Peacock and Rex G Fluharty[4] studied the dynamic relation between storage and circulating iron in normal sub jects and in patients with various hematologic disorders When single tracer doses of radioactive iron (Fe^{5} and Fe^{9}) are given intravenously to man radioiron rapidly enters the hemoglobin cycle and tagged erythrocytes appear in the circulation within 24 hours Thereafter radioactivity of cir culating red cells rises and reaches a plateau in two to three weeks This procedure appears to offer a method of measuring participation of injected iron in the hemoglobin cycle The term utilization curve subsequently used refers specifically to utilization of injected radioiron for hemoglobin production In most experiments Fe^{5} (half life four years) was used Two to three weeks after injection venous blood samples were obtained in the morning and hematologic studies done

Over 15 18 days eight normal controls showed utiliza tion of between 68 and 83 per cent (average 74 per cent) Three patients with diseases not expected to alter iron metab olism (diabetes myocardial infarction and asthma) had utili zation curves similar to the composite curve of normal sub jects

Six patients with acute or chronic blood loss represent ing varying degrees of iron deficiency as shown by the degree of microcytosis and hypochromia showed rapid utilization of injected radioiron Utilization curves of three patients with hemochromatosis confirmed by liver biopsy were depressed in presence of fairly normal red cell produc tion In one patient with refractory anemia and hyperplastic bone marrow one with acute disseminated lupus erythema tosus and aplastic marrow and one with extensive lympho sarcomatous involvement of bone marrow only small amounts of radioiron appeared in peripheral blood Curves of five patients with renal disease and some anemia thought to be due to the uremic state were depressed below normal

(4) Blood 4 905 9 6 A gu t 1949

that life span of erythrocytes may be limited at least in part by changes within the cell which render it more susceptible to destruction by mechanical wear and tear in the circulation It is emphasized however that trauma produced by rolling glass beads may be quite unlike that to red cells in vivo

Decrease in circulating radioactive iron was observed in each experiment soon after mechanical fragility of tagged

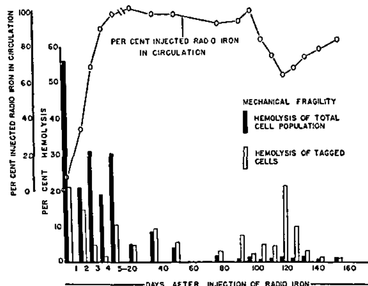


Fig 70 (C t y f St w t W B *t al* J E p M d 91 147 159 F bru ary 1950)

cells began to exceed that of total cell population The lowest point on the curve representing circulating radioiron was noted at 119 119 and 122 days respectively after injection of iron in three experiments Estimates of the life span of dog erythrocytes obtained in this way agree with those provided by other methods

[From these careful observations and from those of Shen and his associates demonstrating increased mechanical fragility of the red cells of patients with certain types of hemolytic anemia (congenital sickle cell disease etc) it is reasonable to assume that this factor is an important one in determining the life of the red cell —Ed]

liver therapy was utilized rapidly and an early plateau reached Utilization curves of two patients with carcinoma were depressed and those of four patients with typical Addison s disease were within normal range

In interpretation of utilization curves there are two important components size of iron stores and bone marrow function Figure 69 depicts the storage and circulating red cell iron in certain conditions as compared with typical radioiron utilization curves In hemochromatosis and iron deficiency the primary factor influencing utilization was size of iron stores In hemolytic anemia and bone marrow dysfunction the chief factor was rate of blood production in bone marrow With a normal rate of blood production changes in percentage utilization reflect alteration in iron stores If storage iron is not greatly altered percentage utilization is determined by function of erythropoietic tissue Rate of erythropoiesis may be estimated by the slope of the utilization curve and evidence of abnormal red cell destruction is found in an early and abrupt plateau of the utilization curve

Age as Affecting Osmotic and Mechanical Fragility of Dog Erythrocytes Tagged with Radioactive Iron W B Stewart J M Stewart M J Izzo and L E Young[6] (Univ of Rochester) administered radioactive iron to three normal dogs two of which had previously been bled in order to tag a group of erythrocytes of approximately known age Osmotic fragility of newly formed tagged cells was significantly greater than that of the general cell population during the first few days after injection of the iron while the mechanical fragility of the young cells was less than that of the general red cell population Figure 70 illustrates the mechanical fragility of tagged dog erythrocytes and of total cell population at various intervals after injection of radioactive iron Circulating radioiron at each interval is expressed as percentage of dose injected As the cells aged and approached the end of the life span their susceptibility to destruction by trauma inflicted by rolling glass beads exceeded that of the general cell population Osmotic behavior of the old cells was not distinctive

Increased mechanical fragility of senescent cells suggests

(6) J E per M d 91 147 159 Febru ry 1950

an optimal concentration of calcium is essential Thromboplastin is also needed Accelerator globulin is a plasma protein which acts as a cofactor of thromboplastin for rapid activation of prothrombin a deficiency may result in a bleeding tendency

Platelets also furnish material which participates in prothrombin activation but contrary to the view held for many years they probably do not furnish much thromboplastin activity The activity is more nearly like that supplied by Ac globulin i e in conjunction with thromboplastin

The exact function of Ac globulin in the clotting mechanism has not been definitely established However several sound experiments indicate that Ac globulin probably participates in prothrombin activation in the following manner First a small amount of prothrombin is activated by calcium platelet accelerator and thromboplastin The small amount of thrombin formed activates plasma Ac globulin Then a rapid interaction of prothrombin thromboplastin calcium platelet *accelerator and active Ac globulin occurs Thrombin is thus* formed rapidly after a slow beginning Quantitative methods have been developed for measuring Ac globulin activity in plasma Such methods reveal that man possesses a lower concentration of Ac globulin than other species The concentration decreases in experimental liver damage *temporarily in dicumarol[*] therapy and slowly in citrated human* plasma after 10 days of storage With large doses of aminophylline Ac globulin concentration in the plasma may double

Under certain conditions calcium thromboplastin Ac globulin platelet derivatives and other factors are prevented from contributing to prothrombin activation by any of several *inhibitors The best known inhibitor is heparin*

The mechanism for clot removal is strikingly similar to the clotting one A plasma substance profibrinolysin is activated to fibrinolysin and this enzyme can dissolve a fibrin clot

Platelet Thrombosis in Human Hemostasis Histologic Study of Skin Wounds in Normal and Purpuric Individuals The importance of blood platelets and platelet thrombosis in the hemostatic mechanism of rats was recently demonstrated In view of the frequency of species variation in anatomy and physiology evidence for or against a comparable role of

Budding of Thrombocytes from Megakaryocytes Previous studies reported that 0 43 75 per cent of megakaryocytes show thrombocyte budding Ronald H Girdwood[7] (Simpson Memorial Inst Ann Arbor Mich) determined the percentage of megakaryocytes showing budding by various technics The accuracy of different technics was evaluated and the actual percentage of such megakaryocytes determined as conclusively as possible

When marrow aspirations were performed using a syringe flushed with sodium citrate a false impression was obtained because many thrombocytes were washed away from parent cells When the dry technic was used results were equally inaccurate because thrombocytes in juxtaposition to megakaryocytes sometimes stuck to them appearing to arise from them When aspirated marrow samples were used best indication of the extent of budding was obtained with a dry technic limiting examination of marrow to areas with definite marrow structure It is concluded that less than 25 per cent of megakaryocytes in normal marrow show true budding at any one time

↓ The following seven abstracts deal with rapidly developing concepts in the field of blood coagulation Other articles with more specific relation to hemorrhagic diseases will be found in appropriate sections —Ed

Blood Coagulation and Practical Significance of Recent Advances in Knowledge of Prothrombin and Ac Globulin are discussed by Walter H Seegers[8] (Wayne Univ) It is advantageous to consider blood clotting as if two mechanisms are provided one involving the interaction of proteins which effects clot formation and one for clot removal

Prothrombin is constantly present in blood if an adequate amount of vitamin K is available for its synthesis by the liver In clot formation prothrombin must first be activated to form thrombin Thrombin reacts with fibrinogen of the plasma to form fibrin which is the clot Calcium tends to have a favorable influence on this process but is not essential Material of platelet origin also makes it much easier for thrombin to clot fibrinogen

In prothrombin activation a number of substances participate calcium thromboplastin accelerator globulin platelet derivatives and other factors For physiologic activation

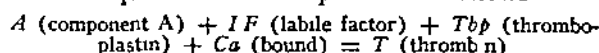
(7) P oc. Soc E per B l & Med 72 192 195 O tober 1949
(8) C culat o 1 2 9 Ja ary 1950

easy reading even in abstract form and the original texts by masters in the field deserve perusal —Ed]

State of Component A (Prothrombin) in Human Blood Evidence That It Is Partly Free and Partly in Inactive or Precursor Form The old classic theory that prothrombin is converted by thromboplastin (thrombokinase) and ionized calcium to thrombin has become untenable because of recent findings A new factor essential for thrombin formation has been discovered It is called the labile factor and is a constituent of both plasma and serum It loses activity when heated and is diminished in stored plasma because of oxidation

During work which led to discovery of the labile factor it was observed that when stored oxalated human plasma was mixed with an equal volume of dog plasma in which prothrombin had been reduced by dicumarol* or adsorbed to aluminum hydroxide the resulting mixture had a prothrombin time shorter than that of fresh plasma Later it was found that human citrated plasma often showed a reduction in prothrombin time after 24 hours of storage No explanation for these findings could be offered until it was recognized that two changes were concurrently taking place in stored plasma a decrease in labile factor and an increase in some other factor which augmented prothrombin activity Owing particularly to development of an assay method for component A (component A of prothrombin probably corresponds to the classic prothrombin) and to discovery of the effect of silicone coated containers on prothrombin activity during storage data have been obtained which not only offer an explanation for the increased prothrombin activity of aged plasma but a new concept concerning the state of prothrombin in blood

From studies based on the prothrombin time of plasma and from data obtained with the adsorption and elution of component A Armand J Quick and Mario Stefanini[1] (Marquette Univ) conclude that formation of thrombin requires component A the labile factor thromboplastin and combined calcium The equation can be expressed as follows



$$A \text{ (component A)} + IF \text{ (labile factor)} + Tbp \text{ (thromboplastin)} + Ca \text{ (bound)} = T \text{ (thrombin)}$$

The reaction appears to follow the law of mass action There is no evidence that any of the factors are accelerators

(1) J Lab & Cl Med 34 1203 1 15 September 1949

platelets in spontaneous human hemostasis would have interest particularly since few observations on man s hemostatic mechanism have been published Technical difficulties in microscopic observation of human vessels during arrest of hemorrhage have not been overcome though observations on animals have been reported

Howard D Zucker[9] (Mount Sinai Hosp New York City) studied serial sections of biopsy specimens of human skin and subcutaneous fat containing puncture wounds after measurement of local bleeding times Specimens were obtained from three patients with normal hemostasis and four with idiopathic thrombocytopenic purpura

Agglutinated platelets arrested hemorrhage in normal skin by rapidly sealing the mouth of all cut vessels larger than capillaries Such platelet thrombi resisted the effective blood pressure in a cut arteriole of 55 μ diameter The puncture tract was normally filled with red cell fibrin clot into which platelet thrombi protruded The red clot sealed the mouth of the few opened capillaries which could be identified Other capillaries may have been sealed by endothelial agglutination Fibrin did not enter or form in injured vessels

Platelet thrombosis was not seen in specimens from patients with idiopathic thrombocytopenic purpura When larger arterioles and venules were cut bleeding was greatly prolonged and fibrin failed to form in the wound because of the speed of blood flow When smaller vessels were cut bleeding time was moderately prolonged but the vessels were eventually sealed by fibrin alone Bleeding time was normal if only capillaries were cut because these were sealed by fibrin

The similarity of histologic appearance described here to that reported after experimental vascular injury in other mammals suggests considerable similarity in mammalian hemostatic mechanisms

Zucker emphasizes that clinical bleeding time tests vary greatly in depth of puncture and in caliber and number of vessels cut Considerable volume of hemorrhage during the first minute is the best guide to an adequate test of the entire hemostatic mechanism

[This article emphasizes the long suspected mechanical importance to hemostasis of platelet agglutination The next four articles do not make

(9) Blood 4 631 645 May 1949

Nature of Action of Labile Factor in Formation of Thrombin was investigated by Armand J Quick and Mario Stefanini (Marquette Univ) It is accepted that in addition to thromboplastin and calcium a third factor is required for thrombin formation It is called the labile factor because it loses activity on storage Prothrombin time is proportionately delayed as this factor is diminished which suggests that thrombin production is reduced However the theoretical objection can be raised that if the factor acts as an accelerator prothrombin activation would only be slowed The procedure developed recently for isolating and assaying free prothrombin by adsorption to tricalcium phosphate and elution with sodium citrate offers a direct approach for determining whether or not the labile factor acts stoichiometrically or as an accelerator The authors therefore devised the following experiment To stored oxalated plasma a fixed excess of thromboplastin an optimal quantity of calcium and varying amounts of labile factor were added Fibrin was removed and prothrombin remaining in the serum was estimated by the adsorption and elution method Thereby the effect of the labile factor on prothrombin consumption was quantitatively determined since the other agents in the reaction were kept constant

Results revealed that when excess thromboplastin and an optimal amount of calcium were added to stored oxalated plasma only a little prothrombin was consumed On adding increasing quantities of labile factor in the form of diluted deprothrombinized rabbit plasma prothrombin consumption was progressively increased This indicates that the role of the labile factor in thrombin formation like that of thromboplastin and calcium is stoichiometric

Role of Calcium in Coagulation of Blood Introduction of two technics using silicone (methylchlorosylone General Electric Dri Film 9987) a film which keeps blood incoagulable without alteration of its properties or lysis of platelets and Amberlite IR 100 (Resinous Products & Co Philadelphia) a resin which quantitatively removes calcium from the blood has offered new possibilities for study of the role of calcium in blood clotting With a combination of these technics it is possible to obtain in vitro blood which differs from that cir

(2) Am J Phy 1 160 572 575 M h 1950

In fresh human plasma component A (prothrombin) is present partly free and partly in an inactive or precursor state which corresponds to the proserozyme of Bordet Activation requires a rough surface but there is no evidence that calcium (as Bordet assumed) thromboplastin or thrombin is essential for conversion to the active state Thus in oxalated human plasma (without ionized calcium) nearly all of component A is changed to the active form after 24 hours of storage if kept in contact with a rough surface such as glass

In coagulation of plasma with a deficiency of available thromboplastin due either to a lack of thromboplastinogen as in hemophilia or to removal of platelets concentration of free component A is greatly increased because little of the original active form is consumed and additional active component A is produced from the inactive precursor

Two types of congenital hypoprothrombinemia are known in which a deficiency of component A occurs In one a true deficiency of both free and total component A exists In the other which is more common and is hereditary concentration of total component A is normal but the amount of free or active component is below normal When these two types of deficient plasma are mixed the prothrombin time of the mixture becomes normal This suggests that a mechanism completely unknown regulates the ratio of active to total component A

The present work confirms early conclusions of Bordet that serozyme or prothrombin may exist in an inactive or precursor state but unlike Bordet s concept that all exists as proserozyme present observations show that a large fraction of total component A is in an active form It appears probable that in a number of recent studies activation of component A has been misinterpreted as an acceleration of conversion of prothrombin to thrombin Since the procedure of the two stage method for determining prothrombin is such that all of component A is converted to the active form this method determines total prothrombin (component A) but does not distinguish between the free and the inactive form The one stage method on the contrary determines the free or active component A and to determine the total all of component A must first be converted to the active state

concluded that combined and not ionized calcium is the fraction active in blood coagulation

Fibrin, a Factor Influencing Consumption of Prothrombin in Coagulation The prothrombin consumption test as originally described determines prothrombin activity remaining in serum one hour after coagulation By means of this test it was established that little prothrombin activity is lost when either platelet poor plasma or hemophilic blood clots These results are explained by postulating that in hemophilia a marked deficiency of thromboplastinogen exists so that only a small amount of prothrombin can be converted to thrombin In thrombocytopenia the platelet enzyme required for activation of thromboplastinogen to thromboplastin is lacking therefore little thromboplastin can become available and consequently little prothrombin is consumed Since the prothrombin consumption test is promising as an important clinical test Armand J Quick and Jean E Favre Gilly[4] (Marquette Univ) attempted to find why at times erratic results were obtained

When normal human blood is allowed to clot and to stand for one hour more than 60 per cent of prothrombin is usually consumed as measured by prothrombin time of serum Serum obtained from clotted blood before retraction occurs has a strikingly short prothrombin time immediately after centrifugation which quickly becomes prolonged showing that there is rapid decrease in prothrombin after separation of serum from the clot If sodium citrate is added to clotted blood before centrifugation the serum obtained has a normal prothrombin time of 11 12 seconds which indicates that the abnormally short prothrombin time of serum immediately after centrifugation is due to a summation of thrombin formed during centrifugation and the amount produced during the prothrombin test

The insignificant consumption of prothrombin in unretracted clotted blood is explained by the rapid and complete adsorption of the freshly formed thrombin by the fibrin clot with its large adsorptive surface that is in intimate contact with the dispersed serum The continuous adsorption of thrombin prevents initiation of the autocatalytic reaction of coagulation which is mediated through the labilizing action

(4) Am J Phy I 158 387 395 S ptembe 1949

culating in vivo only in its complete lack of calcium Addition of measured amounts of calcium under different experimental conditions then permits accurate study of its influence on different phases of coagulation and on the process in toto

Using these new technics Mario Stefanini[3] (Marquette Univ) found the calcium level optimal for coagulation of whole blood or of plasma to be about 1 5 mM practically identical with that of circulating blood that for optimal conversion of prothrombin to thrombin is about 2 5 10 mM Though calcium is the most effective clotting agent its action is not specific since strontium and to a lesser extent magnesium possess similar activity All these cations exercise an inhibitory effect at concentrations higher than the optimal one

All three phases of coagulation appear to be influenced by calcium in artificial experimental conditions Optimal activation of thromboplastin in vitro as expressed by results of the prothrombin consumption test requires a $CaCl_2$ concentration of 8 12 mM optimal action of thrombin on fibrinogen takes place at CaCl levels lower than 5 mM Calcium is most active in the phase of clotting leading to formation of thrombin from prothrombin

Decrease of prothrombin activity due to progressive disappearance of the labile factor and rise of antithrombin activity during storage are closely related to presence or absence of calcium as they are maximum in plasmas made incoagulable with addition of sodium oxalate or sodium citrate 0 02 M or by passage through highly active Amberlite and much less pronounced in plasmas made incoagulable with sodium citrate 0 01 M or by passage through only partially active Amberlite This influence of calcium on the stability of the labile factor seems to indicate existence of a calcium labile factor complex

Stefanini presents evidence that sodium oxalate acts as an anticoagulant not only by precipitating calcium but also by removing the metal from combination with a factor indispensable for blood coagulation and that sodium citrate inhibits coagulation by combining with one or more factors of the prothrombin complex in which it can be substituted by any bivalent cation (Ca Sr Mg) From this evidence it is

(3) Acta med. Scand na 136 250 266 1950

convert prothrombin to thrombin nor clot fibrinogen Furthermore preparations of plasma globulin were said to be separable into two fractions one which promoted clotting and one which exhibited proteolytic activity

Since none of the reported experiments conclusively demonstrated that proteolysis is essential in physiologic clotting of blood the authors made further investigations They prepared a fraction of globulin from human plasma which was deficient in prothrombin thrombin fibrinogen plasma thromboplastin and accelerator globulin but contained considerable potential proteolytic activity which could be activated by streptococcus fibrinolysin This fraction accelerated clotting of normal platelet deficient plasma However the clot accelerating effect of the globulin fraction was the same whether or not its proteolytic property had been activated Addition of streptococcus fibrinolysin to normal platelet deficient plasma did not accelerate coagulation Nor did addition of streptococcus fibrinolysin to hemophilic platelet deficient plasma pro*mote its coagulation*

These data suggest that proteolysis by activated plasma proteolytic enzyme is not an essential stage in blood coagulation The possibility cannot be excluded that the precursor of plasma proteolytic enzyme may promote blood clotting even though it is apparently proteolytically inactive in respect to fibrinogen prothrombin and casein

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HEMOLYTIC ANEMIAS

The following articles are concerned with anemias in which red cell destruction exceeds the capacity of the bone marrow to manufacture them The first three are concerned with erythroblastosis fetalis —Ed

Studies on Preventive and Curative Treatments for Rh Sensitization Rh antibodies are not found preformed but may appear as a result of active or passive sensitization Active sensitization may develop after repeated intravenous or subcutaneous injections of Rh positive blood into an Rh *negative person or as the result of pregnancy* and escape of Rh positive cells of the fetus into circulation of an Rh negative mother Passive sensitization occurs if antibodies from a sensitized mother pass through the placenta into the circula

of thrombin on platelets Fibrin therefore appears to be the most important physiologic antithrombin

It seems clear then that fibrin puts the brake on the autocatalytic reaction of coagulation and keeps it localized to the area in which vascular damage has occurred Paradoxically the fibrin clot which is feared most in thromboembolic diseases is perhaps the most important protection against extension of thromboses beyond the area that requires the thrombi to effect hemostasis It may be postulated that clot retraction in vivo may be dangerous since the extruded serum separated from intimate contact of the adsorptive surface of fibrin will allow thrombin to form which immediately causes extension of intravascular clotting If this assumption is correct factors favoring clot retraction such as anemia and rise in number of platelets increase the danger of progressive intravascular clotting

Studies on Proteolytic Enzyme in Human Plasma Relation between Proteolytic Activity of Plasma and Blood Coagulation Oscar D Ratnoff Robert C Hartmann and C Lockard Conley[5] (Johns Hopkins Univ) point out that evidence has been offered both to support and to deny the hypothesis that *activated proteolytic enzyme of plasma accelerates blood clotting* It has been reported that serum becomes proteolytic after addition of chloroform and again that chloroform treated serum is capable of clotting solutions of fibrinogen The chloroform activated proteolytic property of plasma was shown by one investigator to be present in its globulin fraction Others stated that proteolytic properties of plasma globulin can be activated not only by chloroform but by bacteria free filtrates of cultures of beta hemolytic streptococci A fraction of plasma globulin activated by streptococcus fibrinolysin was found to be thromboplastic hence it was concluded that the proteolytic enzyme of plasma plays a role in blood clotting Further evidence suggesting a relation between proteolysis and coagulation was that inhibitors of trypsin inhibited activity of proteolytic enzyme of plasma and also inhibited blood coagulation

On the other hand certain data cast doubt that proteolysis plays any physiologic *role in clotting In particular it* was reported that purified proteolytic enzyme of plasma did not

(5) J E per M d 91 123 133 F bru ry 1950

the importance of priming It is thought that they should be primed against the bacterial antigen before they have opportunity to be primed against the Rh antigen thus making certain that the vaccine is the more potent antigen Fifty eight patients were multiparas Of the entire group one patient despite countersensitization showed Rh antibodies Nine women sensitized by previous pregnancies were also treated but the practice has been discontinued since experience showed that vaccine therapy was of no avail If the value of vaccine therapy can be established it will be as a preventive measure for those who still show no evidence of sensitization Although the evidence seems to warrant belief that this therapy may reduce incidence of sensitization to the Rh factor it is not infallible More experience is needed

Use of the so called hapten produced by Carter was also studied It is obtained from an ethereal extract of Rh positive cells which is next reduced to dryness and the residue dissolved in alcohol It is assayed for potency by two methods complement fixation and direct inhibition of agglutinins and administered intramuscularly Rh hapten appears to be a lipid substance which does not produce antibodies when injected into the experimental animal To test this material 130 injections were given 11 patients Results were negative

When Rh sensitization is extreme the only recourse for couples desiring children is to adopt a child or resort to artificial insemination from an Rh negative donor or if the husband is heterozygous to take the chance that the next baby may be Rh negative If sensitization is mild it may be possible to save the baby by inducing labor prematurely and giving the infant exchange transfusion without delay

Erythroblastosis Fetalis Value of Blood from Female Donors for Exchange Transfusion In reviewing 208 cases of erythroblastosis fetalis treated by exchange transfusion Fred H Allen Jr Louis K Diamond (Harvard Univ) and Joseph B Watrous Jr[8] (Boston Lying in Hosp) noted that although mortality was 15 1 per cent in the whole group no deaths occurred in the 42 babies who received blood from female donors exclusively This finding prompted statistical analysis of the available data in this large series

In 179 cases blood was used exclusively from male donors

(8) New Engl J Med 241 799 806 Nov 24 1949

tion of the fetus Lester J Unger[6] (New York Univ Bellevue Med Center) reports on efforts made to meet the problem of active sensitization by the Rh factor

New rules have been established for selection of donors for transfusion Rh positive blood should be given to all Rh positive patients (except newborn infants with erythroblastosis due to Rh sensitization) Only Rh negative blood should be given to all Rh negative females from birth to the climacteric For Rh negative women after the climacteric and for Rh negative males of any age Rh positive blood may be given when necessary provided it is recognized that Rh antibodies may develop and provided subsequently the proper pretransfusion tests are performed If sensitization results only Rh negative donors may be used for all subsequent transfusions

The problem of sensitization due to pregnancy is not as simple as the similar problem with transfusion Three methods of treating the mother were studied (1) repeated partial replacement transfusions (2) countersensitization with bacterial vaccines and (3) treatment with hapten It seemed reasonable that repeated partial replacement transfusions might possibly reduce or at least prevent a rise of titer of antibodies in the blood of a mother sensitized by the Rh factor To test this method four women were treated All showed Rh antibodies in the serum two had anti Rh agglutinins and two had Rh blocking antibodies In each case 500 cc blood was withdrawn and 500 cc transfused and repeated until the total amount decided on had been removed and replaced Amount varied from 6 500 cc in 11½ weeks to 21 000 cc in 14½ weeks In no case was there appreciable change in Rh anti body titer despite use of these enormous amounts of Rh negative blood

The second mode of therapy undertaken was that of countersensitization Because of experimental evidence supporting the theory of competition of antigens because of lack of danger with use of typhoid and pertussis vaccines and because any immunity developed by the mother would be of value to the infant clinical trial was begun two years ago At present 93 Rh negative women have been or are being treated by countersensitization Even though the first pregnancy is nearly always spared 26 primiparas were treated because of

(6) Am J Ob t & Gy 58 1186 1 00 D mb r 1949

of the newborn Adult plasma or serum causes pronounced agglutination of red cells which are coated with the blocking antibody It is thought therefore that transfusion of erythro blastotic children with adult s whole blood may be contrain dicated because the infused adult plasma may activate the in complete antibody present in the baby

On the basis of this reasoning Pennell treated 28 patients with erythroblastosis fetalis by transfusion of compatible sedimented red cells from bank blood Three (10 7 per cent) died The mortality rate compares favorably with that in other reports on exchange transfusion

Transfusion of sedimented red cells to the erythroblastotic infant has a number of advantages Severe anemia is overcome by a comparatively small volume (50-60 cc) of cells which cannot overburden the infant s circulatory system The pro cedure for administering the sedimented cells is simple can be carried out via a scalp vein in 15 20 minutes does not re quire special equipment or specially trained transfusion teams and is available wherever there is a blood bank Furthermore it eliminates *administration to the infant of large amounts of* extraneous substances such as sodium citrate heparin and calcium gluconate which are employed in exchange trans fusion The amount of adult plasma which sedimented red cells contain is about 5 per cent and is probably much too small to cause activation of any agglutinins which might be present in the infant The fact that the infant s coated cells are allowed to remain seems of no consequence

Hereditary Nonspherocytic Hemolytic Anemia There are three well known and well defined types of hereditary hemolytic anemia hereditary spherocytosis sickle cell anemia and Mediterranean anemia In addition several other types of inherited anemia have been identified in recent years [The author gives appropriate references to these in the orig inal article —Ed] William H Crosby[1] (Brooke Gen l Hosp Fort Sam Houston) studied a form of hereditary nonsphero cytic and normochromic hemolytic anemia transmitted as a mendelian dominant and associated with brachyphalangia and porphyria Attention was directed to the family through one of its members a soldier

Blood of 35 of the patient s relatives was examined A

(1) Blood 5 233 2 3 M h 1950

(137 cases) or from female donors (42 cases) Of the 137 babies who received blood from male donors only 27 died (19 7 per cent) All 42 who received blood from female donors survived The difference in mortality rates is statistically significant Analysis of other factors such as sex of the infant severity of illness the mother s anti Rh titer and length of gestation showed that no other factor could be held responsible for the benefit of blood from female donors Though further statistical data may possibly not substantiate these results the present study indicated that the beneficial effect of a large amount of blood from female donors in babies with erythroblastosis fetalis is statistically striking In addition to the original series of 179 13 babies with erythroblastosis fetalis were deliberately treated with exchange transfusion using blood from female donors There were no deaths The beneficial component of such blood is unknown but isolated plasma fractions are being investigated It appears that for the present exchange transfusion using blood from a female donor is the treatment of choice

Treatment of Erythroblastosis Fetalis by Transfusion with Sedimented Red Cells is reported by Samuel Pennell[9] (Maimonides Hosp Brooklyn) Treatment by exchange transfusion is predicated on the suppositions that (1) if Rh antibodies particularly of the incomplete or blocking variety can be demonstrated in the mother ante partum the child when born will usually have severe erythroblastotic disease (2) replacement of the affected infant s blood at birth with normal blood by exchange transfusion removes the passively transferred antibodies and the child s damaged red cells thus avoiding hemolysis and arresting progress of the disease In the light of more recent information these hypotheses appear to need re evaluation Rh negative mothers showing high Rh antibody titers ante partum may give birth to Rh positive infants in whom severe erythroblastosis does not develop even though Rh antibodies derived from the mother can be demonstrated both attached to their red cells or circulating freely in their plasma Incomplete or blocking Rh antibodies require an activator which is supplied by both human serum and bovine albumin to effect agglutination of red cells This activator is diminished to an ineffectual level in the plasma

(9) Blood 5 107 12 F bru y 1950

after splenectomy and four months after operation the count had risen to 45 per cent in the peripheral blood and to 56 per cent in the bone marrow In tests which involved mechanical vacuum and osmotic injury the patient s cells showed normal resistance Fragility tests which involved incubation showed uniformly an increased sensitivity of the patient s cells as compared with those of normal controls but compared with those of spherocytic controls the sensitivity was not so great Cross incubation experiments showed the patient s cells to be equally sensitive in his own serum or that of a group com patible control Preliminary heating of the serum for 10 min utes reduced the hemolytic potency about 50 per cent It could not be reactivated by addition of guinea pig complement This observation suggests presence of a heat labile hemolytic fac tor in serum to which the patient s red cells were sensitive Such a reaction rather than a structural weakness may be the basis of the short survival time of red cells in this dis ease The patient s cells survived only 12 days when trans fused into a normal compatible recipient When normal com patible cells were transfused into the patient attrition oc curred at a normal rate Neither degree of anemia nor rate of hemolysis was favorably influenced in the patient by splenec tomy

Of the hereditary anemias this disease seems most closely to resemble hereditary spherocytosis Yet differences of cellu lar survival in vivo and in vitro and failure of splenectomy in hereditary nonspherocytic hemolytic anemia suggest a differ ence in the hemolytic mechanism Demonstration of porpho bilinogen in this patient suggests a possible relation of this hereditary hemolytic anemia to hereditary porphyria

Acute Hemolytic Anemia Due to Naphthalene Poisoning was observed in four children aged 2 2½ by Wolf W Zuelzer and Leonard Apt (Wayne Univ) All patients had eaten or sucked moth balls containing naphthalene Initial symptoms were listlessness and anorexia followed by emesis fever ab dominal pain and pallor Icterus and splenomegaly were either absent or mild Hemoglobinuria was observed in three pa tients The basic pathologic process was a severe acute hemo lytic anemia evidenced by low hemoglobin level erythrocyte count and hematocrit with increased erythrocyte saline fra

(2) J A M A 141 185 190 Sept 17 1949

reticulocyte count was used as a screening test since persons with familial anemia may have a normal red cell count Physical examination was performed on those persons showing reticulocytosis who consented to it After short fingers were encountered several times it was recognized that brachyphalangia was also a familial characteristic With the information obtained it was possible to construct a fair pattern of the disease as it affected members of this family There was a low grade normochromic anemia which did not vary greatly in intensity from one person to another Slight jaundice was also present Affected men were all heavy laborers unaware of their jaundice and unhampered by their anemia Spleen was enlarged in all instances Liver was enlarged in older persons the degree of enlargement apparently increasing with age Bouts of abdominal pain with onset always after age 20 had been experienced by most of those with anemia The reason for pain was not clear In two persons gallstones had been diagnosed yet removal of the gallbladder in one case did not end the abdominal pain There was no history of leg ulcer nor except for a cerebrovascular accident in the grandfather had there been thrombotic or hemorrhagic incidents

Genetic study revealed that the anemia and deformity of the hands were transmitted as mendelian dominant characteristics In no instance had an unaffected person transmitted either trait to his offspring Though these abnormalities did occur in the same person they also occurred independently and were not genetically linked Neither condition was sex linked It appeared that anemia was somehow associated with blood group A since each person with demonstrated anemia was of that group Genetic linkage cannot account for association of group A blood and anemia

Red cells on stained spreads appeared normally filled with hemoglobin Morphologically the cells were normal biconcave disks In the patient and other affected members of the family the following procedures were negative test for abnormal hemolysins and agglutinins including the Coombs antiglobulin test for incomplete antibodies tests for cold agglutinins and cold hemolysins and the Ham acid fragility test for paroxysmal nocturnal hemoglobinuria Before splenectomy the iron stain showed less than 0 1 per cent siderocytes in the patient s peripheral blood Siderocytes gradually increased

probably the direct action of absorbed naphthalene on the red cell membrane

[Emerson and Ham have shown that the hemolytic action of certain coal tar drugs is due to the formation of oxidant derivatives which in vitro cause increases in the osmotic and mechanical fragility of the red cells —Ed]

Marchiafava Micheli Syndrome (Paroxysmal Nocturnal Hemoglobinuria) John Marks[3] reports 3 cases and reviews the 73 previously reported The Marchiafava Micheli syndrome is one of the rarer types of hemoglobinuria characterized by the usual features of hemolytic anemia with hepatosplenomegaly and bouts of hemoglobinuria A distinctive feature is that the hemoglobin is either present in urine only during sleep or else increases greatly during sleep as compared with waking The patient s cells are hemolyzed by his own and by normal serum and the reaction is sensitive to changes in pH This specific serologic test is known as Ham s test

The disease is neither hereditary nor racial nor is it related to occupation Males and females are affected equally The disease may begin at any age but is commonest between 20 and 40

The disease does not always present primarily with hemoglobinuria Presenting symptoms in the 73 cases recorded in the literature were hemoglobinuria in 33 cases jaundice in 27 anemia or dependent symptoms in 36 lumbar pain in 7 abdominal pain in 5 and splenomegaly in 2 It is clear therefore that in hemolytic anemia absence of hemoglobinuria does not exclude the Marchiafava Micheli syndrome It is advisable to include the specific serologic test in investigation of any obscure hemolytic anemia irrespective of the presence of hemoglobinuria

Cause of the disease is unknown The primary fault appears to be in the erythrocytes there being no evidence of inherent abnormality in the serum Autogenous cells are hemolyzed by autogenous serum and by normal serum to the same extent whereas autogenous serum does not hemolyze normal red cells Previous exposure to cold is not necessary to initiate hemolysis The hemolytic reaction is sensitive to changes in pH within the range of changes which may occur in the body The hemolysin is thermolabile and heated serum will inacti

(3) Q rt J M d 18 105 1 1 Ap 1 1949

gility reticulocyte count and nucleated red cells Leukocyto sis anisocytosis poikilocytosis microcytosis spherocytosis and free hemoglobin in plasma were always noted There was pronounced fragmentation of red blood cells (Fig 71) Heinz bodies in erythrocytes were seen in blood smears in the one case in which a search was made on admission

Results of tests for isoagglutinins autoagglutinins cold agglutinins cold and warm hemolysins were negative No in



F g 71 —Blood m (W ght t) h w g r d f gm t t of e yth ocyt \ t g l tl e f f gm t d ll th or t t f h mo gl b n s d nd th f t t f th pp te d (Co t y f Z l er W W d Ap t L J A M A 141 185 190 S pt 17 1949)

fectious process was found in the children and all recovered after blood transfusions Splenectomy is contraindicated If hemoglobinuria is present alkalinization of the urine may be indicated It is difficult to differentiate this disease from Led erer s anemia unless a history of naphthalene ingestion is elicited

Similar changes were obtained in dogs fed naphthalene appearance of Heinz bodies preceding onset of hemolytic ane mia Heinz bodies were also produced by exposing normal canine erythrocytes to plasma of dogs fed naphthalene

The mechanism of the intravascular hemolysis which is the cause of the acute anemia of naphthalene poisoning is

bins of normal persons and of persons with sicklemia and sickle cell anemia This report deals largely with an electro phoretic study of these hemoglobins

Results indicate that a significant difference exists between electrophoretic mobilities of hemoglobin from erythrocytes of normal persons and from those of persons with sickle cell anemia The two types of hemoglobin are easy to distinguish as the carbonmonoxy compounds at pH 6 9 in phosphate buffer of 0 1 ionic strength In this buffer the sickle cell an emia carbonmonoxyhemoglobin moves as a positive ion whereas the normal compound moves as a negative ion there is no detectable amount of one type present in the other The hemoglobin from erythrocytes of persons with sicklemia however appears to be a mixture of normal and sickle cell anemia hemoglobins in roughly equal proportions The elec trophoretic difference between normal and sickle cell anemia carbonmonoxyhemoglobin also exists in the ferrohemo globins Experiments with a buffer different from the phos phate demonstrated that the difference between the hemo globins is essentially independent of the buffer ions

The most plausible hypothesis for the cause of the differ ence in mobilities is that a difference in number or kind of ionizable groups exists in the two hemoglobins Experiments indicated that sickle cell anemia hemoglobin has 2-4 more net positive charges/molecule than normal hemoglobin Stud ies have been initiated to elucidate the precise nature of this charge difference and it appears probable that normal and sickle cell anemia hemoglobin have different globins

Since hemoglobins in sickle cell anemia and sicklemia erythrocytes are different from those present in normal red cells it appears probable that the hemoglobins are responsible for the sickling process The mechanism of the sickling process may be pictured as follows It is proposed that a surface re gion on the globin of the sickle cell anemia hemoglobin mole cule is absent in the normal molecule and has a configura tion complementary to a different region of the surface of the hemoglobin molecule The fact that sickling occurs only when partial pressures of oxygen and carbon monoxide are low sug gests that one of these sites is near the iron atom of one or more of the hemes and that when the iron atom is combined with either of these gases the two structures are complemen

vate normal serum Hemolysis increases greatly during normal sleep whatever the time of day An increase in blood acidity during sleep has been suggested as the salient feature of the disease although the evidence is contradictory Hemolysis may be inhibited in vitro by presence in plasma of the following substances sodium citrate potassium oxalate potassium cyanide and heparin Concentration of the ions of some of these substances changes during sleep and these changes rather than pH changes may be responsible for the nocturnal character of the hemoglobinuria

No cure has been reported and no treatment has given lasting improvement Although the reason is unknown para sympathomimetic drugs seem to decrease the hemoglobinuria and therefore seem worthy of further trial The course is irregularly downhill over 7 10 years with death usually from intercurrent infection Splenectomy is contraindicated the operation has a 40 per cent mortality and has never been re ported to cure In addition to the acid serum hemolysis test of Ham the heat test of Hegglin and Maier is a specific test for Marchiafava Micheli syndrome [because during incubation glycolysis increases acidity of the blood —Ed]

Sickle Cell Anemia A Molecular Disease Erythrocytes of certain individuals possess the capacity to undergo reversible changes in shape in response to changes in partial pressure of oxygen With lowered pressure these cells change from the normal biconcave disk to crescent holly wreath and other forms a process known as sickling About 8 per cent of American Negroes possess this characteristic usually they exhibit no pathologic consequences and are said to have sicklemia or sickle cell trait However in about 1 in 40 a severe chronic anemia results from excessive destruction of erythrocytes this is sickle cell anemia The main observable difference between erythrocytes of sickle cell trait and sickle cell anemia is the greater reduction in partial pressure of oxy gen required for sickling of a major fraction of trait cells than for anemia cells Because evidence indicated that sickling may be intimately associated with the state of hemoglobin in the erythrocyte Linus Pauling Harvey A Itano S J Singer and Ibert C Wells[4] (California Inst of Technology) compared the physical and chemical properties of hemoglo

(4) Science 110 543 548 Nov 5 1949

blood counts were possible only when warm pipets and diluting fluid were u ed Mild hypochromic anemia developed

In February 1948 salicylate therapy (5 2 Gm sodium salicylate daily in divided doses) was begun with the hope of blocking antigen antibody reaction At this time cold agglutinin titer was 1 20 480 One week later the titer was 1 10,240 and plasma salicylate level 24 8 mg /100 cc Subsidence of titer was difficult to evaluate how ever because of a sudden period of warm weather and improvement was not maintained

It is suggested that the primary mechanism responsible for symptoms due to presence of cold hemagglutinins is intra vascular clumping of erythrocytes The precipitating factor is presumably cold This possibility should be considered in cases of bilateral gangrene in which exposure to cold alone has not been severe enough to produce this pathologic process Local thrombosis of a deep part is more difficult to explain but the primary mechanism is thought to be probably the same Hemoglobinuria results whenever tubular absorption falls behind filtration rate

Use of salicylates was suggested by experimental work on animals given sodium salicylate orally and at the same time immunized by intravenous injections of bacteria Such rabbits showed diminished complement fixing antibodies agglutinins and hemolysins when compared with controls Anti Rh agglu tinin formation in guinea pigs and rabbits is reduced when sodium salicylate is administered before and during immu nization with rhesus monkey blood cells It has also been shown that when typhoid vaccine is given patients receiv ing massive salicylate therapy antibody formation is sup pressed

[A cold hemolysin was not excluded as the cause of hemoglobinuria and anemia in Case 2 because the Donath Landsteiner test was not per formed Howeve the hemolysis in this patient was probably due to the increased mechan cal fragil ty of the cold agglutinated red cells by the high titer of the plasma cold agglutinin as experimentally demonstrated by others in such patients —Ed.]

Developing (Coombs) Test in Spherocytic Hemolytic Anemias Its Significance for Pathophysiology of Spherocy tosis and Splenic Hemolysis The developing (Coombs) test using an anti human globulin rabbit serum demonstrates globulin antibodies adsorbed to the surface of erythrocytes Thus coated and uncoated red cells can be distinguished Karl Singer and Arno G Motulsky[6] (Michael Reese Hosp

(6) J Lab & Cl M d 34 768 783 J 1949

tary to a considerably diminished degree The sickle cell anemia hemoglobin molecules might then be capable of inter acting with one another at these sites sufficiently to cause at least a partial alinement of the molecules within the cell with the result that the erythrocyte becomes birefringent and the cell membrane is distorted to accommodate the now relatively rigid structures within its confines

[Our associate John W Harris has just demonstrated that 15 25 per cent solutions of deoxygenated hemoglobin from sickle cells exhibit increase in viscosity birefringence and tactoid formation These are di rect evidences of molecular alinement and aggregation —Ed.]

Symptoms Attributable to Cold Hemagglutination Report of Two Cases is made by Jeanne C Bateman[5] (Washington D C) Presence of cold hemagglutinins should be suspected when there is difficulty in blood counting procedures or cross matching of blood at room temperatures or when acrocyano sis hemolytic anemia and hemoglobinuria follow exposure to cold As pointed out by Stats and Wasserman gangrene may develop if exposure is prolonged Less commonly thrombotic phenomena are manifest

CASE 1 —Man 22 was hospitalized with complaints of a chilly feeling fever malaise increasingly severe nonproductive cough and dyspnea There were moist rhonchi and fine rales in both lung fields Cultures of blood and sputum were negative White cell count was 6 500 Twelve hours after he was placed in an oxygen tent signs and symptoms of thrombophlebitis developed in the superficial veins of the right leg It was noted that the oxygen tent was unusually chilly The patient gradually recovered At no time did he receive sulfonamide therapy Cold hemagglutinin titers were 1 1,280 the 6th day after admission 1 2 560 the 11th day and 5 weeks later had dropped to 1 640

CASE 2 —Man 43 first experienced purplish blue mottling of face ears and fingers after exposure to cold in November 1944 Symptoms were followed by passage of red urine The patient s con dition was diagnosed as kidney disease and he was at bed rest for two months Symptoms reappeared when he was permitted to go outdoors but subsided during the following summer only to reap pear with onset of cold weather There was no history of primary atypical pneumonia or of other viral infection Physical examina tion was essentially noncontributory except for demonstration of acrocyanosis following exposure to cold

In April 1946 when he was first seen by Bateman cold hemag glutination titer was 1 2 621 440 During the next two years there was a wavelike decline in titer with a tendency for titer to be lowest during the summer However thermal range remained so wide that

(5) Arch. I t. Med. 84 523 531 Octobe 1949

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(6) J Lab & Cl M d. 34 768 783 J 1949

Chicago) report 16 cases of hereditary and acquired spherocytic hemolytic anemia studied with antiglobulin serum All seven with idiopathic acquired type and one with symptomatic hemolytic anemia (reticulum cell sarcoma) gave a positive reaction It was negative in one patient with hemolytic anemia caused by a sulfonamide Of the seven patients with hereditary spherocytosis six showed a negative reaction and one severely ill patient had a strongly positive reaction Splenectomy in the acquired disease resulted in disappearance of the coated spherocytes or the coated cells remained demonstrable although the pathologic hemolysis ceased Splenectomy in the patient with hereditary spherocytosis and a positive Coombs reaction led to disappearance of the coating although spherocytosis persisted This demonstrated that two different mechanisms were operating in this case

A positive reaction indicates presence of immune bodies The immune bodies which occur in spherocytic anemias are qualitatively different from the antibodies directed against Rh Hr antigens

Existence of coated and uncoated spherocytes is explained by the hypothesis of the multiple origin of spherocytes In the hereditary type of hemolytic anemia uncoated cells develop in the marrow under genetic control whereas in the immunologic variety spherocytes are formed after contact with coating antibodies originating in the spleen and/or other organs Spherocytosis caused by physical and chemical factors results from exposure of normal red cells to these agents either intravascularly or within damaged tissues

The theory of specific splenic hemolysis is advanced to explain the role of the spleen in spherocytic hemolytic syndromes in contrast to the current hypotheses of hypersplenism According to the hypothesis of specific splenic hemolysis the spleen participates little if at all in physiologic red cell disintegration Recent studies have shown that physiologic erythrocyte elimination depends on cell age and the mechanical factors to which it is exposed during its life span within the circulation All hemolytic syndromes are characterized by erythrocytes with specific structural alterations of the cytoskeleton Such changes may manifest themselves either morphologically or functionally Splenic hemolysis is predominantly involved in the spherocytic hemolytic

syndromes In the hereditary disorder the spleen selectively removes the uncoated pathologic cells In the immunologic acquired variety the spleen produces the coating antibodies which it is assumed injure the cells and thus render them spherocytic Conceivably the cells may then be destroyed in the spleen by an increased concentration of antibodies in this organ

It is well known that patients with acquired hemolytic anemia may or may not respond to splenectomy whereas pa tients with the hereditary disorder almost always benefit

DEVELOPING TEST IN HEMOLYTIC ANEMIAS

P Reacti o

A. Acquired spherocytic hemolytic anemias
  1 Idiopathic
  2 Symptomatic (Hodgkin s disease leukemia, lymphomas Boeck s sarcoid Gaucher s di ea e * ovarian tumors * etc)
B Hereditary spherocytosis (occa sionally)
C Isoimmunization due to known immune bodies Rh, Hr A B (M*)
  1 Erythroblastosis fetalis
  2 Sensitization following transfusion

Neg t ve Rea n

A Hereditary pherocytosis
B Spherocytic anemia due to phys ical or chemical factors (burns sulfonamides phenylhydrazine*)
C Sickle cell anemia
D Cooley's anemia
E Paroxysmal nocturnal hemoglo binuria

A md nb f th d

Patients with the acquired disorder may be classified into three groups according to their response to splenectomy In the first group spherocytes disappear completely and perma nently In the second the coated cells persist pathologic hemolysis stops and the spherocytes have a normal life span in the patient and even when transfused into a normal person. In the third group coated spherocytes continue to be destroyed rapidly These different responses require an explanation

In the first group antibody production is apparently re stricted to the spleen A persistently positive Coombs reaction after splenectomy indicates that antibodies are manufactured in other organs as well The fact that splenectomy stops the pathologic hemolysis in some of these patients and does not in others may perhaps be explained on a quantitative basis If formation and release of damaging immune bodies pro ceed on a larger scale in extrasplenic tissues splenectomy will

Chicago) report 16 cases of hereditary and acquired spherocytic hemolytic anemia studied with antiglobulin serum All seven with idiopathic acquired type and one with symptomatic hemolytic anemia (reticulum cell sarcoma) gave a positive reaction It was negative in one patient with hemolytic anemia caused by a sulfonamide Of the seven patients with hereditary spherocytosis six showed a negative reaction and one severely ill patient had a strongly positive reaction Splenectomy in the acquired disease resulted in disappearance of the coated spherocytes or the coated cells remained demonstrable although the pathologic hemolysis ceased Splenectomy in the patient with hereditary spherocytosis and a positive Coombs reaction led to disappearance of the coating although spherocytosis persisted This demonstrated that two different mechanisms were operating in this case

A positive reaction indicates presence of immune bodies The immune bodies which occur in spherocytic anemias are qualitatively different from the antibodies directed against Rh Hr antigens

Existence of coated and uncoated spherocytes is explained by the hypothesis of the multiple origin of spherocytes In the hereditary type of hemolytic anemia uncoated cells develop in the marrow under genetic control whereas in the immunologic variety spherocytes are formed after contact with coating antibodies originating in the spleen and/or other organs Spherocytosis caused by physical and chemical factors results from exposure of normal red cells to these agents either intravascularly or within damaged tissues

The theory of specific splenic hemolysis is advanced to explain the role of the spleen in spherocytic hemolytic syndromes in contrast to the current hypotheses of hypersplenism According to the hypothesis of specific splenic hemolysis the spleen participates little if at all in physiologic red cell disintegration Recent studies have shown that physiologic erythrocyte elimination depends on cell age and the mechanical factors to which it is exposed during its life span within the circulation All hemolytic syndromes are characterized by erythrocytes with specific structural alterations of the cytoskeleton Such changes may manifest themselves either morphologically or functionally Splenic hemolysis is predominantly involved in the spherocytic hemolytic

Repeated blood examinations revealed severe macrocytic anemia with erythrocyte counts of 1 000 000 1 500 000 and hemoglobin value of 3 5 5 5 Gm There was reticulocytosis of 25 50 per cent and a raised mean corpuscular volume *Reaction to the Coombs test* was positive and cold autohemagglutinins were present to a titer of 1 512 at 2 C there was just perceptible autohemagglutination at 37 C Plasma bilirubin level was raised

Hemolysis continued at an extremely rapid rate and blood trans *fusions were of only transient benefit Hemoglobinuria was generally* absent but was observed on several occasions after transfusions Data obtained by the differential agglutination technic confirmed that transfused blood was rapidly eliminated.

It was repeatedly found that normal group O erythrocytes and the patient s own corpuscles underwent hemolysis in vitro in the patient s serum The hemolytic antibody seemed to be di tinct from the cold hemagglutinin antibody and was absorbed onto corpuscles bett r *at 37 C than at lower temperatures Amount of hemolysis* was largely determined by pH of the corpuscle serum suspension Hemolysis was maximal at about pH 6 8 7 0 and was inhibited below pH 6 and above pH 8 there was but a trace of hemolysis in un acidified serum This restri ted pH hemolysis range seemed due to the hemolysin s being poorly absorbed at the alkaline side of neu trality When graded amounts of acid were added to serum it could be hown that the pH range within which hemolysis could be ob *served corresponded closely to that in chronic hemolytic anemia with* nocturnal hemoglobinuria

Although the cause was obscure there can be little doubt that this patient had a severe idiopathic acquired hemolytic anemia The abnormal hemolysis in the patient s serum was an unusual feature It is probably only in the severest forms of hemolytic anemia when autoantibodies are being formed *in* large amounts that there is sufficient for detention in serum over and above that absorbed onto the patient s own cor puscles This probability and the fact that adjustment of pH to an optimum for hemolysis is important in demonstration of hemolysins of the type described perhaps accounts for the rarity of similar observations

Acquired Hemolytic Anemia Relation of Erythrocyte Antibody Production to Activity of Disease Significance of Thrombocytopenia and Leukopenia are discussed by Rob ert S Evans and Rose T Duane[8] (Stanford Univ) It has been increasingly evident that acquired hemolytic anemia is caused by a hemolysin active for all erythrocytes whereas congenital hemolytic jaundice is due to a defect in red cell

(8) Blood 4 1196 1213 N mb 1949

not be successful However understanding of these mechanisms is too incomplete to rule out the possibility that qualitative differences in coating antibodies and their associated damage to the cytoskeleton may not also be of importance

Demonstration of a positive reaction to the Coombs test in hereditary hemolytic anemia diminishes the value of this test in differential diagnosis between hereditary and acquired spherocytic anemia Since a positive reaction indicates an immunologic mechanism a negative reaction speaks strongly for familial spherocytosis if drugs and other obvious hemolytic agents can be ruled out The table summarizes the disorders in which performance of the developing test may be of diagnostic value The authors believe that the developing test is essential in diagnosing hemolytic syndromes If the reaction is positive the hemolytic anemia should be designated as of the immunologic type Such an immunologic hemolytic anemia may even be superimposed on hereditary spherocytosis

[We are in substantial agreement with this excellent article However it is not necessary to assume that because globulins are adsorbed on red cells they are antibodies In many instances substances have an avidity for the red cell merely because of a particular molecular structure e g certain viruses The Coombs test tells us only that a globulin is adsorbed The reason it is there may be quite different in different diseases The strongly positive Coombs reaction in the single case of congenital hemolytic jaundice may readily be interpreted as evidence of a superimposed acquired process —Ed]

Hemolysins in Acquired Hemolytic Anemia Effect of pH on Activity in Vitro of Serum Hemolysin Hydrogen ion concentration has a controlling effect on many hemolytic systems both simple and complex Effect of pH or carbon dioxide concentration on activity in vitro of hemolytic antibodies of human origin has seldom been considered except in the case of chronic hemolytic anemia with nocturnal hemoglobinuria in cold hemoglobinuria and in a case of acute hemolytic anemia in infancy J V Dacie[7] (Postgraduate Med School of London) reports observations on the activity in vitro of an abnormal hemolysin in the serum of a patient with idiopathic acquired hemolytic anemia and the effect of pH on its action

Girl 18 severely ill was hospitalized with signs of intense hemolysis Splenectomy had been performed for hemolytic anemia about five years before Cause of the original hemolytic attack was uncertain family history did not suggest a familial incidence

(7) Bl od 4 928 934 Augu t, 1949

like agent in all The data are summarized in the table Diagnosis of hemolytic anemia was based on presence of chronic anemia reticulocytosis an increase in serum bilirubin and in most patients demonstration of increased fecal urobilinogen In most instances patients did not exhibit well marked spherocytosis and increased osmotic fragility In further dis

TYPICAL HEMATOLOGIC DATA IN RELATION TO AGGLUTINABILITY OF ERYTHROCYTES IN DILUTIONS OF ANTIGLOBULIN SERUM

Patient No	Stage of Disease	Hematocrit	% Reticulocytes	Icterus Index	Fecal Urobilinogen mg	Greatest Dilution of Antiglobulin Serum Showing Agglutination
1	Active	21	8.0	30	2080	1—320
	Quiescent post splenectomy	41	1.2	5	125	1—20
2	Active	28	27.0	100		1—640
3	Active	26	18.0	20	450	1—160
	Spontaneous remission	36	12.0	10		1—10
4	Active disease after splenectomy	17	7.0	40		1—160
5	Active disease after splenectomy	26	20.0	50	700	1—320
6	Quiescent after splenectomy	40	1.0	10		1—40
7	Active	23	12.0	10	1560	1—320
	Quiescent 3 mo post splenectomy	33	1.6	8	220	1—1
8	Active	34	13.0	20	1800	1—80
	Spontaneous remission	45	1.0	10		1—5
9	Quiescent 18 mo post splenectomy	47	0.5			1—5
10	Quiescent 12 mo post splenectomy	42	4.0		506	1—5
11	Active	28	22.0	50		1—640

tinction to congenital hemolytic jaundice rapid destruction of normal transfused cells was evident in seven patients (Fig 72)

The sensitizing agent was found to be adsorbed on erythrocytes when it could not be demonstrated in serum The amount adsorbed was assayed roughly by making serial dilutions of the antiglobulin serum With this technic a fairly consistent correlation was found between the amount of antibody on the cell and activity of the disease Splenectomy when successful exerted a curative effect by sharply reducing amount of antibody substance on the cell Two patients entered spontaneous remission after a long period of activity Onset of re

structure During the last few years it has been possible to demonstrate sensitization of erythrocytes from patients with acquired hemolytic anemia with immunologic technics devel oped in the field of Rh sensitization There is some evidence by analogy that the hemolytic agent in acquired hemolytic anemia is an immune body similar to the univalent or hyper immune Rh antibody and may be a response to antigen stimulus

The destructive agent appears to be a fraction of plasma protein probably a globulin similar to the univalent or hyperimmune Rh antibody Because accelerated hemolysis proceeds at a fairly constant rate in acquired hemolytic an emia it appears that the agent does not require special condi tions of temperature or pH for activity The sensitizing agent can be removed from the surface of the red cell by heating a suspension of sensitized cells in normal saline The immune body appears to remain active to some degree in the saline eluate because normal cells exposed to it become agglutinable in the Coombs reagent The agent is thought to be active for all erythrocytes because transfused cells seem to be destroyed at a rate which approximates rate of destruction of native cells

Although the etiologic significance of the antibody like abnormality in acquired hemolytic anemia seems established study of patients who appeared to have recovered completely following splenectomy showed persistence of the abnormality Erythrocytes from patients in remission were agglutinable in anti human globulin serum though all evidence of accelerated hemolysis had subsided This suggested that the agglutin ability of erythrocytes in the various mediums could be the result rather than the cause of the disease and that splenec tomy produced a remission by removal of the principal site of destruction of abnormal cells On the other hand it seemed that a quantitative relation between the amount of immune body present and the rate of blood destruction might better explain the apparent paradox The authors therefore at tempted to devise a method of quantitating the amount of anti body on the red cell so that measurements could be made dur ing active and quiescent phases of the disease

Observations on 11 patients with acquired hemolytic anemia showed sensitization of erythrocytes by an antibody

PERNICIOUS AND OTHER NUTRITIONAL MACROCYTIC ANEMIAS

This title is intended to include instances of pernicious and related macrocytic anemias defined by their response to purified liver extract and to vitamin B 12. Other macrocytic anemias fail to react to these agents but do respond to crude orally administered liver extract or to pteroylglutamic acid Recently evidence has been put forward to suggest that the megaloblastic anemia of infancy may be due to a combined deficiency of pteroyl glutamic and ascorbic acids It is possible that the so called citrovorum factor which may be the biologically active form of pteroylglutamic acid, requires ascorbic acid for its formation in the body —Ed

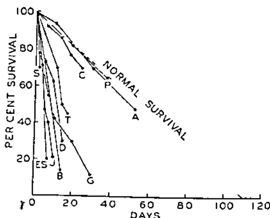
Hemopoietic Activity in Pernicious Anemia of Beef Muscle Extract Containing Food (Extrinsic) Factor on Intravenous Injection without Contact with Gastric (Intrinsic) Factor Previous observations had shown that 200 Gm beef muscle is hemopoietically active in addisonian pernicious anemia when 150 ml normal human gastric juice is given by mouth simultaneously If an acid mixture of beef muscle and gastric juice is incubated 12 hours and then neutralized it also is active On the other hand if the incubated mixture is heated to 100 C for five minutes its hemopoietic activity as determined by oral administration is destroyed whereas that of whole liver or liver extract is not detectably affected by such a procedure From this it was assumed that the thermostable anti pernicious anemia principle of liver was not formed by the incubation procedure in vitro and that heat merely destroyed a thermolabile factor in gastric juice

If a beef muscle and gastric juice mixture is given at an acid pH (1 8 3 5) after incubation no hemopoietic effect appears whereas if treated with alkali to give pH of 5 7 it is active This suggested that a preliminary chemical interaction occurred between the so called extrinsic factor of beef muscle and the intrinsic factor of normal human gastric juice at or about neutrality within the intestinal tract

Because of this evidence the increased hemopoietic activity in pernicious anemia of liver and of relatively crude liver extracts when given orally with human gastric juice was originally assumed to indicate the presence of extrinsic factor as well as of the anti pernicious anemia principle However it was later shown that even refined liver extracts and pure

mission in both was associated with decrease in amount of adsorbed immune body However in one patient antibody production returned without immediate recurrence of hemolytic anemia This inconsistency is not understood

That definite and sustained leukopenia with neutropenia and thrombocytopenia occurred in several patients with hemolytic disease due to an immune body agent raises questions as to etiology of classic thrombocytopenic purpura and splenic



F g 72—Su l tım of t sf d lls n pat nts w th h m lyt c and p t ents w th th r type f h molyt d se e P t nts *S ES J B T* d *G* h w d e t atı of yth yt pat nts *C P* and *A* h d co g nıt l l lyt c j undice M d te an n m nd pa xy mal nocturn l h m gl b (C t y of E ns R S a d Duan R T Bl od 4 1196 1 13 N embe 1949)

neutropenia Some patients observed seem to have transition forms between acquired hemolytic anemia and thrombocytopenic purpura Sensitized platelets may be susceptible to agglutination and phagocytosis and the presence of an antiplatelet antibody in the circulation may damage the cytoplasm of the megakaryocyte so as to inhibit the formation of platelets

[This last is interesting in view of the demonstration by Ackroyd (this YEAR BOOK p 442) of platelet agglutination in the plasma of patients exhibiting thrombocytopenic purpura due to sensitization to sedormid®—Ed]

sorption of glucose l tyrosine or digestion products of casein

[Subsequent observations continue to point to vitamin B only as the material potentiated by gastric juice—Ed]

Antianemia Activity of Fecal Extract from Pernicious Anemia Patient Microbiologic assay has shown that patients with untreated pernicious anemia excrete in feces substances which act as growth factors for Lactobacillus lactis Dorner *the organism used for assay of vitamin B_{12} Four substances* in liver have been found to be active for this organism and one of these thymidine failed to induce a remission in a case of pernicious anemia S T E Callender B J Mallett G H Spray and G E Shaw[1] therefore attempted to find whether the substances active for L lactis Dorner in feces of untreated pernicious anemia patients were also effective against the anemia

When 5 ml of a properly prepared extract of feces was injected intramuscularly daily for five days into a patient with untreated pernicious anemia an optimal reticulocyte response *and rise in hemoglobin occurred and the marrow previously* megaloblastic changed to normoblastic Chromatography of the extract suggested that the antipernicious activity was due to vitamin B_1 itself

[Bethell has made similar observations Because Girdwood ha own that the daily fecal output contains about 0 5 *mg* of pteroylglutamic acid unless known to be absent it may have been involved in these results —Ed]

Decrease of Renninogenuria in Pernicious Anemia and Its Diagnostic Value in Liver Treated Patients was studied by Ole Sylvest[2] Externally secreting glands lose some of their secretion into the blood stream and this secretion is excreted in the urine When *such glands* become acutely inflamed *they* often become leaky and larger quantities of secretion pass into the blood and thus into the urine (e g the diastasuria in parotitis and pancreatitis) Conversely it is to be expected that when these glands are atrophied the secretion will be reduced In atrophy *of the pepsin and rennin producing glands* in the gastric mucosa excretion of pepsin and rennin in the urine must therefore be supposed to decrease or cease

Atrophy of the gastric glands occurs in pernicious *anemia* Histologic changes in the stomach are most pronounced in the

(1) L t 2 57 J ly 9 1949
(2) Acta m d S d 133 346 349 1949

vitamin B_{12} derived from liver when given by mouth were potentiated in their hemopoietic effect by gastric juice

Observations reported here by Frank H Gardner John W Harris Robert F Schilling and William B Castle[9] (Boston) concern questions obviously raised by these findings Can extrinsic factor alone (beef muscle) act directly as the anti pernicious anemia principle i e is a suitable preparation of beef muscle such as vitamin B_1 hemopoietically effective in pernicious anemia on parenteral administration without contact with gastric juice? Is the hemopoietic potentiating action of intrinsic factor specific only for vitamin B_1 and chemically similar substances in beef muscle and in other foods or does intrinsic factor also facilitate nonspecific absorption or otherwise enhance hemopoietic action of other substances?

Observations were made during successive periods of 10 or more days on seven patients with addisonian pernicious anemia A 70 per cent alcohol extract of beef muscle was the source of food (extrinsic) factor When 10 ml extract was given daily by mouth to these patients a detectable reticulocyte response appeared in only one instance When the extract was given with normal human gastric juice to four patients reticulocyte responses appeared in all when the material was subsequently given intravenously without gastric juice to three of these patients another reticulocyte response appeared indicating greater hemopoietic activity

In two patients it was shown that hemopoietic effect of 10 ml beef muscle extract on daily intravenous injection was less than that of daily intramuscular injection of 1 μg crystalline vitamin B_{12} Microbial assays indicated that 10 ml beef muscle extract contained 0 37 0 9 μg vitamin B_{12} activity

Judging from previous observations on the potentiation of crystalline vitamin B_1 by normal human gastric juice the hemopoietic activity of the beef muscle extract when given orally with gastric juice appeared surprisingly great However only this fact suggested that substances in the meat extract other than vitamin B_1 were susceptible of potentiation by normal human gastric juice on oral administration in pernicious anemia No evidence was obtained for a nonspecific effect of gastric (intrinsic) factor in increasing hemopoietic action of pteroylglutamic acid or in promoting intestinal ab

(9) J L b & Cl M d 34 1502 1511 N emb r 1949

sore tongue indigestion and weight loss occurred and anemia recurred She complained of abdominal discomfort and distention and of paresthesia in the hands and feet Some months later she was hospitalized. Slight clubbing of fingers edema of legs and glossitis were present There was a swelling apparently composed of firm coils of bowel in the center of the abdomen and peristalsis was visible and noisy Blood study showed hemoglobin 9 4 Gm erythrocytes 2 630 000 color index 1.2 reticulocytes 1 6 per cent and leukocytes 3,200 Sternal puncture revealed an active marrow with both normo- and megaloblastic hemopoiesis There were 12 per cent megaloblasts and 21 per cent normoblasts in the film. A fractional test meal revealed free hydrochloric acid and barium meal study evidence of relative small bowel obstruction with hypermotility Plasma protein was 4 17 Gm per cent.

Treatment consisted of a low fat high protein diet with yeast and proteolyzed liver extract by mouth Plasma protein rose to 6 1 Gm per cent and edema diminished. As a preliminary to operation transfusion of 2 pt blood was given The previous anastomosis was identified 1 in above the ileocecal valve The excluded coil of bowel which was about 2 ft long contained several strictures and the intervening musculature was greatly dilated and hypertrophied. The mesentery was thickened as in regional ileitis but the bowel wall was not so rough and appeared whiter than in this disease The excluded loop was resected and side to side anastomosis performed

Recovery was good Liver extract was administered parenterally and despite relapse of anemia once after therapy was discontinued because of sensitization and again after an emotional upset four years after surgery the patient was symptom free and the red cell count had been maintained

[In view of the work of Janet Watson suggesting intestinal bacteria presumably in the colon may compete for available vitamin B_{12}, it seems possible that a small intestinal loop could greatly enhance this competition. —Ed]

Pernicious Anemia and Related Anemias Treated with Vitamin B_{12} Edgar Jones William J Darby and John R Totter[4] believe that vitamin B_1 should be used in daily doses *of 3 μg during the first six weeks of treatment of pernicious* anemia and thereafter in daily doses of 1 μg In some patients other factors may be necessary to obtain maximal erythrocyte levels These conclusions are based on personal experience with eight patients and the reported experiences of others

Reticulocyte count was an unreliable quantitative criterion of the adequacy of therapy Often amounts of vitamin B_{12} or liver extract sufficient to produce maximal reticulocyte response failed to produce red cell regeneration

Vitamin B_{12} pteroylglutamic acid and liver extract each

(4) Blood 4 827 844 J ly 1949

hydrochloric acid and pepsin producing area of fundus glands

With a method previously described by the author the renninogen in the urine of 25 normal persons 30 with pernicious anemia and 9 with another kind of gastric achlorhydria was determined Those with pernicious anemia showed no values above 0 3 rennin units/10 ml urine In the normal group values for persons aged 17-46 ranged from 0 6 to 2 8 rennin units and for those aged 63 77 from 0 1 to 1 5 units Histamine administration caused no consistent increase in urine rennin concentration in normal persons

If values above 0 3 rennin units are found in 10 ml of morning urine it is likely that the patient does not have pernicious anemia

Clinical Association of Macrocytic Anemia with Intestinal Stricture and Anastomosis D G Cameron G M Watson and L J Witts[3] (Radcliffe Infirm Oxford England) review 60 cases from the literature and report 1 case Peripheral blood smears were identical with those of patients with addisonian pernicious anemia and bone marrow studies revealed some degree of megaloblastic change Gastric analysis however often showed free acid Steatorrhea was not commonly found and it seems unlikely that resection was an important factor because in no case was more than 60 cm of intestine removed The cause of anemia in these patients is not understood but macrocytic anemia has occurred in rats after blind loops of small intestine were produced surgically It may be that toxic compounds are formed in such loops which interfere with erythropoiesis In some rats anemia responded to injections of liver extract Liver therapy was used in *27* of the 61 patients with success in *22* In several surgical correction of the intestinal abnormality led to cure of anemia

Woman 42 whose mother was known to have pernicious anemia presented symptoms of subacute intestinal obstruction Relief from abdominal symptoms followed anastomosis of adjacent loops of ileum A year later she again became ill and was found to have severe hyperchromic anemia with a hemoglobin value of 5 9 Gm per cent and an erythrocyte count of 1 690 000 Blood film showed macrocytosis anisocytosis and poikilocytosis Treatment with an oral liver preparation was effective

Four years later she was unable to obtain oral liver extract and was given a preparation intramuscularly Despite intensive therapy

(3) Blood 4 793 80 J ly 1949

sore tongue indigestion and weight loss occurred and anemia recurred. She complained of abdominal discomfort and distention and of paresthesia in the hands and feet. Some months later she was hospitalized. Slight clubbing of fingers, edema of legs and glossitis were present. There was a swelling apparently composed of firm coils of bowel in the center of the abdomen and peristalsis was visible and noisy. Blood study showed hemoglobin 9.4 Gm, erythrocytes 2,630,000, color index 1.2, reticulocytes 1.6 per cent and leukocytes 3,200. Sternal puncture revealed an active marrow with both normo- and megaloblastic hemopoiesis. There were 12 per cent megaloblasts and 21 per cent normoblasts in the film. A fractional test meal revealed free hydrochloric acid, and barium meal study evidence of relative small bowel obstruction with hypermotility. Plasma protein was 4.17 Gm per cent.

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Vitamin B_{12}, pteroylglutamic acid and liver extract each

(4) Blood 4: 827-844, July 1949.

reduced the fecal urobilinogen output possibly by decreasing urobilinogen formation by promoting formation of less fragile red cells or by decreasing urobilinogen formation in some nonhemopoietic tissue

Because no change in urinary excretion of pteroylgluta mate or of porphyrin was detected in patients given vitamin B_1 it is inferred that the effect of this vitamin does not de pend on great release of pteroylglutamic acid

The authors also gave vitamin B_1 to one patient with nu tritional macrocytic anemia one with sprue and one with anemia associated with intestinal lipodystrophy Erythropoi etic response was satisfactory in all In two patients mild neurologic involvement was relieved by vitamin B_{12} alone

Vitamin B_1 is regarded as the third chemically distinct substance demonstrated to possess hemopoietic activity pter oylglutamic acid and thymine being the other two

[In our experience it is certainly not necessary to give daily doses of purified liver extract or of vitamin B to promote excellent hematologic and clinical remissions After the first sure signs of response weekly in jections will suffice for the next six weeks when blood regeneration will usually be reasonably complete Thereafter we give injections once a month at the rate of 1 U S P unit a day —Ed]

Variable Response to Vitamin B_1 of Megaloblastic Anemia of Infancy is reported by Calvin W Woodruff How ard W Ripy J Cyril Peterson and William J Darby[5] (Van derbilt Univ) The term megaloblastic anemia has been used to designate normocytic or macrocytic anemia in infancy and childhood characterized by megaloblastic arrest of bone mar row The disease responds to liver extract or to pteroylglu tamic acid Isolation from liver of another hemopoietic sub stance vitamin B_1 and demonstration of its effectiveness in pernicious anemia provides an additional tool for study of megaloblastic anemia Available information indicates that 1 μg B_1 possesses hemopoietic activity in pernicious anemia of approximately 1 U S P unit of purified liver extract A single dose of 25 μg is usually followed by a maximal reticu locytosis in pernicious anemia

The authors report excellent response in two patients with megaloblastic anemia of infancy treated with vitamin B_1 a third patient showed no hematologic response but later re sponded well to folic acid Hematologic response of the first

(5) P d t i 4 7 3 29 D mb 1949

two patients to vitamin B_{12} was in all respects comparable with that obtained with folic acid or liver extracts

Experience with these three patients suggests that the megaloblastic anemia of infancy may be not a single entity but rather a syndrome some cases of which may respond to one of the newer hemopoietic vitamins while other cases respond to another

[Agreed. The first two patients probably had a limited intake of vitamin B The third judging from recent observations by Luhby and by May had a deficient intake of folic acid or one made inadequate by a controlling deficiency of ascorbic acid —Ed]

Effect of Animal Protein Factor Concentrate on Persons with Macrocytic Anemia of Pernicious Anemia of Nutritional Macrocytic Anemia and of Sprue, and on Persons with Nutritional Glossitis For 15 years investigators have been working intensively on an illusive vitamin or a complex of closely related factors found in association with proteins of animal origin For a number of years there has been evidence that soya bean meal was not adequate as the only source of protein in poultry feeds Hatchability of eggs produced by hens fed these diets was low whereas this defect could be remedied by feeding meat scraps With isolation of vitamin B_{12} a long sought for antipernicious anemia factor of liver investigators reported that it possesses animal protein factor activity for the chick and concluded that it is identical with or closely related to the animal protein factor from other sources

Tom D Spies Guillermo Garcia Lopez Fernando Milanes Robert E Stone Ruben Lopez Toca Tomas Aramburu and Sam Kartus[6] therefore studied the effectiveness of an animal protein factor concentrate produced by micro organisms (supplied by Dr T H Jukes of Lederle Laboratories Inc) in five cases of pernicious anemia four of nutritional macrocytic anemia three of nutritional glossitis and three of tropical sprue After baseline determinations were completed animal protein factor concentrate was injected in amounts ranging from a total of 5 cc in 23 days to 5 cc daily for 14 days

Intramuscular injection of animal protein factor concentrate in pernicious anemia nutritional macrocytic anemia and tropical sprue was followed by a positive hematologic response in each case Parenteral administration in nutritional glossitis unassociated with anemia led to disappearance of

(6) Blood 4 819 8 6 July 1949

redness and soreness of the tongue The limited amount of clinical biologic and chemical evidence available in studying animal protein factor might suggest that this substance is identical with vitamin B_1 More complete evaluation is needed

[Similar results in pernicious anemia have been reported by Stokstad and his associates —Ed]

Pteroyl Polyglutamic Acids in Treatment of Pernicious Anemia The remarkable therapeutic and hematologic results obtained with folic acid in treatment of pernicious anemia naturally suggested that folic acid deficiency played a part in etiology of this disease consequently some workers suggested that patients with pernicious anemia were able to utilize only the parent folic acid and not the pteroyl polyglutamates from which it is normally formed Because of conflicting reports as to whether patients with pernicious anemia can utilize folic acid conjugates and the bearing of these results on etiology of pernicious anemia John F Wilkinson and Martin C G Israels[7] (Univ of Manchester) extended their studies using two synthetic folic acid conjugates pteroyl tri γ glutamic acid (teropterin®) and pteroyl di α glutamic acid (diopterin®)

Thirteen patients with pernicious anemia were treated Eight were given teropterin® alone via intravenous intramuscular and oral routes All had normal responses with reticulocytosis and subsequent increases of red cells and hemoglobin Three were given diopterin® alone intravenously and intramuscularly Doses available were minimal but all three had reticulocyte responses and reasonable increases of red cells and hemoglobin Two patients were given diopterin® and then teropterin ® one responded poorly to diopterin® but well to teropterin ® and the other responded satisfactorily to both

The authors conclude that patients with pernicious anemia can hydrolyze and utilize folic acid conjugates (pteroyl poly glutamic acids) whether of a naturally occurring γ amino type like teropterin ® or an α amino type like diopterin ® which does not occur in nature There is thus no reason to suppose that in pernicious anemia there is a failure to release free folic acid from its conjugated form

[Since it is known that the synthetic mono glutamic acid commonly employed under the name of folic acid or pteroylglutamic acid is effective in pernicious anemia in 0 5 1 0 mg amounts daily it would have been

(7) Lanc t 2 689 691 O t. 15 1949

more meaningful had these observations not been conducted with such huge doses as 100 mg at a single injection —Ed.]

Studies in Pernicious Anemia Patients Treated with Liver Extract and Folic Acid Antagonists Leo M Meyer Norton D Ritz Anthony Caccese Julius Rutzky Arthur Sawitsky and George Bock[8] (New York City) found that folic acid antagonists do counteract the erythropoietic effect of liver extract in patients with pernicious anemia The dose of folic acid antagonist necessary to prevent reticulocytosis and increase in hemoglobin and red cells varied in different patients In one patient 40 mg met fol B (methyl pteroic acid) daily had only a partial effect whereas 200 mg daily resulted in no reticulocyte response and a stationary blood picture for one month After discontinuance of the drug further administration of liver extract was followed by slow rise in hemoglobin and red cells but no reticulocytosis Another patient also had a weak reticulocyte response with an actual fall in hemoglobin and red cells necessitating transfusion when given 40 mg of antagonist daily and 10 units of liver extract Adequate liver therapy and 60 mg of antagonist daily were followed by no reticulocytes or change in peripheral blood count After the antagonist was discontinued and repeated liver extract injections were given there was a slow rise in red cells and hemoglobin but no reticulocyte response was ever evoked A third patient had a similar course After administration of 20 units of liver extract there was complete absence of reticulocyte response and fall in hemoglobin and red cells with only 40 mg of antagonist for four days Injection of 10 units of liver extract produced no change in hemoglobin red cells or reticulocytes Administration of 10 units of liver extract on each of two successive days one week later resulted in a slow increase in hemoglobin and red cells and a very poor reticulocyte response A fourth patient came under observation during a satisfactory reticulocytosis Administration of 200 mg met fol B for 16 days had no apparent effect on reticulocytes but hemo lobin and red cell count remained practically unchanged After the drug was discontinued for 15 days blood count rose slowly The fifth patient was treated with an fol R (pteroylaspartic acid) a less potent folic acid antagonist than met fol B and sulfadiazine was

(8) Am J M S 218 197 03 A gu t 1949

administered to prevent liberation of folic acid in the small intestine Although satisfactory reticulocyte response oc curred after 10 units of liver extract no change in hemoglobin and red cells took place In three of these patients pronounced megaloblastosis followed treatment with folic acid antagonists even though they received adequate liver therapy All patients uniformly appeared ill and complained of weakness fatigue and somnolence while receiving either antagonist Ap parently the drug had a continued effect because after discon tinuance patients felt badly had no reticulocyte reactions and no clinical improvements were noted

An additional patient with pernicious anemia in relapse was treated with 200 mg met fol B daily for 14 days but was given 10 and 15 γ vitamin B_{12} on the 3d and 11th days and 5 mg a methopterin (4 amino 10 methyl pteroylglutamic acid) intramuscularly No clinical remission or reticulocyte response occurred hemoglobin red and white cell counts did not rise and sternal aspirations revealed megaloblastosis of 11 23 per cent on four occasions

It is concluded that lack of hematologic response in pa tients with pernicious anemia in relapse treated with adequate doses of liver extract and a folic acid antagonist suggests that pteroylglutamic acid is necessary for production of red blood cells

Idiopathic Steatorrhea (Nontropical Sprue) with Megalo blastic Anemia Liver treatment for tropical and nontropical steatorrhea with macrocytic anemia has been recommended for many years though the response is unpredictable A new line of approach was provided by reports on the effect of folic acid in the West Indian form of tropical sprue which stated that there was remission of megaloblastic anemia and relief from such symptoms as sore tongue anorexia and passage of bulky fatty stools However the number of adequately studied patients is small

M C G Israels and J Sharp[9] (Manchester) therefore re port on five patients who had megaloblastic anemia refractory to liver treatment Three of them were also refractory to vita min B_1 All responded both clinically and hematologically to folic acid

(9) La cet 1 752 756 Apr 22 1950

In these patients the disorder was characterized by progressive and often severe anemia infantilism mild finger clubbing and skin rashes of a deficiency type megaloblastic change in marrow usually free HCl in gastric juice and defective absorption of fat from the bowel Defective fat absorption may be difficult to detect unless specially looked for If missed diagnosis is likely to be refractory megaloblastic anemia None of these patients was known to have steatorrhea at onset of anemia and in two there were few symptoms to suggest the diagnosis One patient was originally thought to have *idiopathic refractory megaloblastic anemia it responded satisfactorily* to folic acid A year later the patient relapsed and for the first time had fatty bulky stools with fat absorption of only 59 per cent Diagnosis was changed to idiopathic steatorrhea In another patient original diagnosis was achrestic anemia and it was five years before fatty diarrhea disclosed the true diagnosis A 12 day test is essential for accurate assessment of quantitative changes in fat absorption and *if correct diagnosis is to be reached at an early stage*

There is now sufficient evidence that there are some patients with megaloblastic anemia whose blood picture responds well to liver extracts vitamin B_1 and folic acids and that a second group responds to folic acids but not to parenteral liver extracts or to vitamin B_1 Addisonian pernicious anemia and nutritional macrocytic anemia as seen in America and the West Indies are in the first group the second group *comprises tropical and nontropical sprue pernicious anemia* of pregnancy and possibly most patients with nutritional megaloblastic anemia in other parts of the world The authors stress that if there are megaloblastic marrow and free acid in gastric juice the next step irrespective of gross appearance of stools or normal values for fat content of a single fecal specimen should be a fat balance test Only in this way can the few patients be detected for whom folic acid is the treatment of choice

[Even simpler to proceed with carefully controlled administration of folic acid with several reticulocyte counts during the first 10 days of therapy —Ed]

Allergic Reactions with Parenteral Liver Therapy and Vitamin B_1 Bengt Noren[1] (Univ Hosp Upsala) studied

(1) A t med S d 137 48 65 1950

130 patients with pernicious anemia treated with liver parenterally 24 (18 per cent) of whom had allergic reactions Since six had been known previously to be highly sensitive to injectable liver extracts and had therefore been specially chosen for this study 18 per cent may be an exaggeration of the actual number of allergic patients Thirty seven patients had positive skin reaction to one or more commercially prepared liver extracts given intracutaneously and 23 of these showed clinical allergy with manifest symptoms after therapeutic doses of liver extracts The other 14 were classified as latently allergic. One patient with manifest allergic symptoms after liver injections gave negative skin reactions to all extracts used Study of the antigenic properties of liver extracts revealed that the organ specific type of allergy was more common than the species specific (27 and 10 respectively)

Skin tests with chemically pure vitamin B_{12} were performed on nine patients all of whom had strongly positive skin reactions to several commercial liver extracts The original solution contained 0 025 mg/ml This was diluted 1 10 and 0 05 ml was injected intracutaneously If the full therapeutic dose of pure vitamin B_{12} is proved to be about 0 015 mg the injected amount expressed in terms of the necessary active dose was much higher than the injected amount of ordinary liver extract used for testing All patients tested with vitamin B_1 showed negative reactions This fact seems to indicate that allergic reactions to liver given parenterally are not usually caused by the pure antianemic factor itself

Allergic reactions began most commonly during the first year of liver treatment after three years complications of this type were uncommon A hereditary tendency to allergy (atopic constitution) as revealed by close questioning about a positive family history of allergy did not seem to be of importance for development of allergic reactions to liver given parenterally

Noren believes that skin tests are not absolutely decisive since a positive reaction may indicate clinical or latent allergy but negative reactions make the presence of manifest allergy extremely unlikely Intracutaneous methods of testing appeared to be more sensitive than scratch tests but in cases in which scratch tests produced positive reactions clinical allergy was usually present Checking of cutaneous sensitivity

as a routine method in all cases of pernicious anemia is not necessary but should be reserved for special cases

[In our experience no organ specific allergy to liver extract has been *encountered. Invariably a change from extract derived from pork to one* from beef or vice versa has re ulted in complete relief until *in some* instances ensitivity to the other species developed The confusion on this point in the literature seems to arise from attempts to interpret skin tests —Ed.]

HYPOCHROMIC ANEMIA

The following articles are concerned with various aspects of anemias usually but not always econdary to iron deficiency —Ed

Severe Anemia Secondary to Diaphragmatic Hiatus Hernia Report of 20 Cases is presented by Steven O Schwartz[2] (Cook County Hosp) Bleeding from the stomach in these patients resulted in severe iron deficiency anemias There was a paucity of gastrointestinal symptoms but cardiovascular symptoms were prominent Physical examination revealed no significant abnormalities It is suggested that in patients especially women past middle age with an iron deficiency anemia but without a history of bleeding without localizing symptoms and significant physical changes diaphragmatic hiatus hernia should be ruled out before other diagnoses are entertained

Definitive diagnosis of diaphragmatic hernia is based on x ray studies Small or reducible hernias are likely to escape discovery unless the examiner is alert for such clues as (1) displacement of the lower segment of the esophagus (2) tortuous but not dilated terminal esophageal segment (3) angulated segment (4) undue retardation of the barium stream at the hiatus (5) gastric content level above the esophageal aperture (6) differentiation of what apparently is high hourglass contraction of the stomach with a visible niche at the constriction site and which often is a stomach *hernia through the diaphragm* with the ulcer *merely* a complication

In most patients with diaphragmatic hernia bleeding is due to congestion of the mucous membrane and venous enlargement in the walls of the herniated portion of the stomach Ulcers in the herniated portion of the stomach have been

(2) Ill M. J 97 204 210 Apr 1 1950

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placental transfer and is analogous to increase in iron binding capacity of serum in iron deficient states Elevation in plasma copper would seem to be independent of changes in iron since there was no correlation in time or degree between these two values Additional knowledge concerning metabolism and functions of copper is needed before conclusions can be drawn concerning its significance in various clinical conditions

Intravenous Iron in Hypochromic Anemia Associated with Rheumatoid Arthritis was investigated by R J G Sinclair and J J R Duthie[4] (Edinburgh) Hemoglobin levels were measured on 100 consecutive patients with rheumatoid arthritis on admission and discharge from hospital Average hospital stay was six weeks All patients were on the same basic regime which included full diet and vitamin concentrates with extra proteins if necessary Patients with hemoglobin levels below 80 per cent were given iron orally in the form of fersolate beginning with a dose of 3 gr three times daily and *increasing to 6 gr during their stay Hemoglobin levels re* mained below 80 per cent in 12 per cent of these cases The effect of intravenous iron in the patients who did not respond to oral iron was then investigated A test dose of 50 mg ferrivenin was given to exclude patients unduly sensitive to the drug subsequent treatment was five 200 mg doses daily In 16 of 23 patients a satisfactory rise in hemoglobin followed administration of intravenous iron

Intravenous administration of iron is worth a trial in all patients with hypochromic anemia associated with rheumatoid arthritis who do not respond satisfactorily to iron by mouth With daily doses not exceeding 200 mg toxic effects were insignificant

[It is probably even more important not to give a large total amount of iron because of the possibility of producing hemosiderosis The authors policy of a total of 1 Gm seems sensible It should be appreciated however that no significant rise in hemoglobin values could be expected before two weeks at a relatively high initial level On the other hand the iron injections should not simply be continued until that event occurs for it may never appear in the face of chronic infection —Ed]

Iron Overload (Hemosiderosis) Aggravated by Blood Transfusions is reported by E E Muirhead G Crass F Jones and J M Hill[5] (Dallas Tex) Excessive iron deposits in the body are usually placed in one of two categories (1)

(4) La t 2 646 647 Oct 8 1949
(5) A b I t M d. 83 477 501 M y 1949

reported They are the result of trauma and are usually in the lower end of the esophagus near its juncture with the stomach Traumatic ulcers result from to and fro action of the stomach in the hernial ring when the hernia is small and from forceful pressure exerted on the large distorted and congested stomach during attacks of vomiting when the hernia is large

Studies on Free Erythrocyte Protoporphyrin, Serum Iron, Serum Iron Binding Capacity and Plasma Copper during Normal Pregnancy were carried out by Jane Fay G E Cartwright and M M Wintrobe[3] (Univ of Utah) to determine the chemical pattern of the blood in the pregnant state Measurements in 86 normal pregnant women revealed a decrease in packed red cell volume in the latter part of pregnancy There was no significant change in free erythrocyte protoporphyrin although a slight elevation of the mean was found during the latter phase of pregnancy A diminution in serum iron was evident during the latter part of pregnancy and at the same time the iron binding capacity of serum increased Plasma copper values increased during the first trimester and remained elevated during pregnancy Normal values were regained during the first two months post partum Plasma copper values were considerably higher in maternal than in placental blood whereas the converse was true for serum iron

Changes noted during pregnancy differ in certain respects from those observed in various types of anemia Serum iron values in pregnancy did not reach the extremely low levels seen in iron deficiency nor was there the pronounced increase in free erythrocyte protoporphyrin seen in iron deficiency anemia The chemical pattern did not correspond to that observed in the anemia of infection in which an increase in erythrocyte protoporphyrin and a decrease in iron binding capacity of serum occurs

Iron binding capacity is increased during the latter half of pregnancy when demand for iron by the fetus is greatest Present observations reveal a close time correlation between decrease in serum iron and increase in iron binding capacity It may be that elevation in iron binding capacity is part of the mechanism for increased iron absorption mobilization and

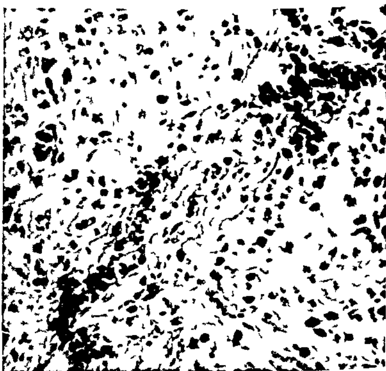
(3) J Cl n In st g t n 28 487 491 May 1949

tients was compared with that of the same type of tissues from 10 patients who died suddenly and in whom there was no apparent abnormality of these tissues Iron content was much higher in the five anemic patients Of interest was the preponderant concentration of iron in the liver In four cases total amount of liver iron approximated the total amount known to have been given in the transfused blood But a preponderance of iron was also observed elsewhere in the body therefore an additional source of iron must exist Absorption by the intestinal mucosa despite an already existing excess seems the most likely source Figure 73 illustrates a section of liver from one of these patients

The types of anemia in the five patients were acquired hemolytic anemia in two aplastic anemia in two one of whom had a pulmonary fungus granuloma and the other a tuberculoid granulomatous nephropathy and in one classic pernicious anemia with repeated relapses due to the patient s failure to maintain liver therapy Each of these anemias is known to be associated with increased plasma iron concentration and with some increase in tissue iron content In these instances tissue iron content however was greatly increased and was of the magnitude ascribed to hemochromatosis In the lungs interstitial fibrosis was prominent accompanied by pneumonitis Excessive liver damage had occurred in three to five cases Kidneys contained iron casts and displayed clinical evidence of functional impairment Hepatitis occurred in three patients and the likelihood of homologous serum hepatitis cannot be excluded Moderate renal insufficiency might be blamed in part on severity of the anemia Explanations other than iron deposits for the observed findings are therefore possible nevertheless it seems that excessive intracellular iron deposits should have adverse functional as well as morphologic implications

Eventual outcome for patients with refractory anemia does not appear good Development of isoimmunization of milder types leads to a shorter and shorter span for infused erythrocytes Greater frequency of transfusions means more iron is being deposited throughout the body The large iron deposits in reticuloendothelial elements may act to produce effects of a reticuloendothelial block thus lowering resistance to infectious agents

Hemosiderosis is characterized by widespread iron deposition associated with prolonged hemolysis or following repeated experimental injection of hemoglobin solution intravenously (2) Hemochromatosis is most often characterized by widespread iron deposition (hemosiderin pigment) hemofuscin



F g 73—S t f l r show g destroyed a d col p d ent l p t on f hep tic l b l d h a y m lat on f on paren h m l d K pff ella. (Co te y of M h d E E r l A ch I t Med 83 477 501 May 1949)

deposits increased copper content of tissues cirrhosis and hypogonadism pancreatic damages and diabetes mellitus and skin pigmentation These features of hemochromatosis vary in intensity and in frequency of their combination

At autopsy five anemic patients who had required transfusions over prolonged periods had widespread iron deposits in various tissues and parenchymatous tissue damage Iron concentration in liver pancreas kidneys and lungs of these pa

time was anti A agglutinin detected in the infant s serum and the red cells gave a negative Coombs reaction. Antibodies in the mother s serum for the five Rh Hr antigens in bloods of type Rh_1Rh_2 could not be demonstrated. Up to age 17 months repeated examination showed the defect in hemopoiesis to be confined to failure of red cell formation Repeated transfusions are necessary to maintain nor mal blood levels

The only causative factor for anemia that can be postu lated in this case is the possibly injurious effect on fetal eryth ropoiesis of the anti A agglutinin elaborated by the mother in an incompatible pregnancy Although the blood disorder at onset of the patient s illness can probably be safely classi fied as erythroblastosis fetalis relationship of the anti A ag glutinin to depression of erythropoietic centers and continu ance of the anemia require elucidation It is conceivable that erythropoiesis in the fetus may be impaired by prolonged re action with an antibody in high titer against its own red cells in the course of an incompatible pregnancy It has been pointed out that the A and B blood agglutinable factors can be demonstrated in the fetus between the second and third month and the possibility of early isoimmunization in the first months of fetal development has been suggested There fore prolonged exposure of red cells and their precursors dur ing a vulnerable period of fetal life to the anti A agglutinin may be responsible not only for anemia at birth but for its persistence in the neonatal period

To test further the hypothesis that erythropoiesis may be come depressed in erythroblastosis fetalis bone marrow was aspirated in several instances of this disease during protracted anemia Individual examinations showed a decreased percent age of nucleated red cells in several cases regardless of whether treatment consisted of subtotal blood replacement or multiple transfusions

Blood and Bone Marrow in Patients with Cirrhosis of Liver were analyzed by Lawrence Berman Arnold R Axelrod Thomas N Horan Samuel D Jacobson Elwood A Sharp and Elmore C VonderHeide[7] (Detroit) on the basis of a re view of the literature and their study of 25 patients with diag noses verified by liver biopsy Complete blood studies with simultaneous aspiration biopsy of sternal marrow obtained

(7) Blood 4 511 528 M y 1949

Chronic Congenital Aregenerative Anemia (Pure Red Cell Anemia) Associated with Isoimmunization by Blood Group Factor A Causative factors of aplastic and hypoplastic anemias include chemical and physical agents infection exhaustion of bone marrow and specific blood dyscrasias and malignant tumors with bone marrow replacement When these factors have been eliminated a relatively rare group of idiopathic aplastic anemia remains which has been attributed to congenitally inferior bone marrow Aplastic anemia is a chronic progressive disease characterized by simultaneous depression of the three principal cellular elements in bone marrow and resulting in a peripheral blood picture of profound anemia leukopenia neutropenia and thrombocytopenia Hypoplastic anemia differs from aplastic anemia in that red blood cell formation is impaired with lesser involvement of granulocytes and platelets When failure of hemopoiesis is restricted entirely to erythrocytes without impairment of leukocytes or platelet production the condition has been designated chronic congenital aregenerative anemia or pure red cell anemia Carl H Smith[6] describes a case in which bone marrow failure was confined to erythropoiesis without simultaneous depression of granulocytes or platelets or their precursors

Boy aged 2 months born three weeks prematurely was hospitalized because of progressive anemia Jaundice developed at age 4 days and did not disappear until the third to fourth week The mother had not been pregnant before and there was no history of hereditary blood disorder On admission there was no jaundice heart and lungs were normal and spleen and liver edge were palpable at the costal margin There were no petechiae or other manifestations of bleeding into the skin Hemoglobin level was 9 5 Gm red cell count 3,500 000 white cell count 13 000 with normal differential count packed red cell volume 24 per cent platelets 290 000 reticulocytes 0 2 per cent bleeding time 3 minutes 35 seconds and clotting time 3 minutes The mother s blood group was O Rh positive and that of the infant and father A Rh positive Clinical course and hematologic features appeared similar to those of mild erythroblastosis fetalis perhaps due to isoimmunization of the mother by the offspring Tests of the infant s saliva showed him to be a nonsecretor The mother s anti A serum titer reached a maximum of 1 128 000 At no

(6) Blood 4 697 705 J 1949

megaloblastic anemias and the macrocytic anemia of cirrhosis as peripheral blood study does not provide evidence of the type of erythropoiesis in marrow

Combined study of peripheral blood and sternal bone marrow may lead the clinician to serious consideration of cirrhosis of the liver Macrocytosis or macrocytic anemia without hypochromasia plus lymphopenia and thrombocytopenia with normal or increased marrow cellularity and normal or increased erythrocytogenesis and megakaryocytogenesis constitutes a hematologic picture which points strongly to cirrhosis of the liver When anemia is absent and the other signs are present the probability of cirrhosis is even greater

The authors conclude that combined blood and sternal marrow study is useful in establishing diagnosis of cirrhosis of the liver in patients in whom other diseases have obscured its manifestations or in whom historical evidence is absent so that clinical diagnosis is difficult

[The many points distinguishing this anemia from pernicious anemia, which it may superficially resemble should be noted —Ed]

Blood and Bone Marrow Studies in Renal Disease Irwin R Callen and Louis R Limarzi[8] (Univ of Illinois) studied peripheral blood and bone marrow in 102 patients with nephritis related diseases and hypertension In 44 patients with renal disease of sufficient severity to produce azotemia degree of anemia definitely increased as nonprotein nitrogen rose Abnormalities in other blood values such as chloride CO_2 combining power glucose and albumin and globulin could not be correlated with degree of anemia nor could the degree of anemia be correlated with level of nitrogenous waste products in the blood Review of these patients histories failed to show that albuminuria or a deficient protein diet had any effect on the anemias Hematuria was seen in many patients without anemia and in some with anemia There was no correlation between hematuria and anemia Of the 44 patients with anemia and azotemia 81 per cent had a normocytic normochromic anemia Peripheral blood smears revealed no significant abnormalities

This study has shown that anemia is rarely present in cases of renal disease unless there is an associated elevation of nitrogenous waste products in blood It is however generally

(8) Am J Cl P th 20 323 J ry 1950

within ½ 24 hours before the liver specimen was removed were carried out on all patients

Principal blood findings were macrocytic or normocytic anemia with normal or elevated mean corpuscular hemoglobin values lymphopenia and thrombocytopenia in most cases Bleeding was not an essential factor in production of anemia in cirrhosis and severity of anemia or macrocytosis did not appear to be related to severity of the liver lesion

A consistent change in bone marrow was extension of the marrow organ so that active hemopoiesis was found in the shafts of long bones Regardless of the presence or absence of bleeding or anemia the sternal marrow was usually of normal or increased cellularity with normal or increased erythrocytogenesis and megakaryocytogenesis Hypocellularity of the marrow was unusual even in patients with advanced liver lesions Macronormoblastic erythropoiesis was seen in patients with macrocytic anemia but megaloblastic erythropoiesis did not result from cirrhosis of the liver

Presence of peripheral cytopenias (anemia and thrombocytopenia) despite normal or increased formation of erythroblasts and megakaryocytes in the marrow was suggestive of hypersplenism in patients with hepatic cirrhosis In patients with chronic hemorrhage blood and bone marrow pictures were those of iron deficiency anemia although other changes such as lymphopenia and thrombocytopenia tended to persist

Changes described cannot be considered pathognomonic of cirrhosis even though they appear to be characteristic of the disease On the other hand it is not justifiable to consider complete blood and bone marrow studies as valueless and without diagnostic importance in cirrhosis In patients known to have the disease appearance of microcytic hypochromic anemia or micronormoblastic marrow indicates chronic blood loss Hypocellular marrow in patients with macrocytic anemia suspected of having cirrhosis is unusual and should point to other or additional factors in the clinical picture Although normocytic or macrocytic anemias are compatible with diagnosis of cirrhosis macrocytic hypochromic anemia as determined by mean corpuscular volume and mean corpuscular hemoglobin values is not typical and should lead to further study of the patient Marrow examination may be of crucial importance in distinguishing between pernicious or other

are most common in cases of splenomegaly in older patients It is now generally accepted that bone marrow rather than the spleen or peripheral blood is primarily at fault The chief argument is whether the changes are reactive or neoplastic

John P Wyatt and Sheldon C Sommers[9] (Boston) studied 30 cases to find clues to the origin morphology and nature of this clinicopathologic montage Twenty autopsies were per

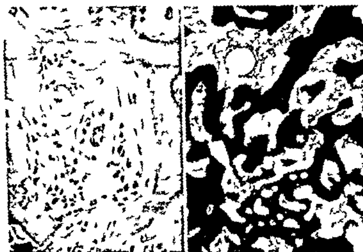


Fig 74 (left) — [illegible] 50

Fig 75 (right) — [illegible] 50

(Courtesy of Wyatt J P and Sommers S C Blood 5 39 347 April 1950)

formed Salient observations were as follows Necrosis of partly matured erythroid and myeloid bone marrow cells appeared to be the fundamental primary lesion Reactive overgrowth of surviving usually more immature cells followed Extramedullary hemopoiesis identical with that in other diseases developed Integrity and eventual overgrowth of reticular and stromal tissues were uniformly visible in marrow and sites of myeloid metaplasia Hemopoietic cells occasionally underwent violent hyperplasia but the invasive property

(9) Blood 5 3 9 347 Ap 1 1950

accepted that a mild or moderate anemia is present in patients with chronic glomerulonephritis who have impaired kidney function but no azotemia the implications being that disturbed kidney function is a factor in production of the anemia This is not in keeping with results in this group Of 22 patients having chronic glomerulonephritis without azotemia (azotemia being defined as a blood nonprotein nitrogen level above 40 mg per cent) 10 had mild anemia There was only one instance of anemia in a patient with chronic nephritis who had no elevation of blood nitrogen values when first studied or during three years observation It seems safe to say that anemia is not related to proteinuria is not present in nephrosis without azotemia and is not related to damaged kidney function per se

Normal cellularity or hypercellularity of bone marrow was observed in most patients with nephritis irrespective of its stage In at least 80 per cent of those with azotemia bone marrow was hypercellular mainly myeloid and megakaryocytic cells being involved Erythropoiesis was normal Only after nonprotein nitrogen reached 150 mg or more did bone marrow show any quantitative evidence of a moderate hypoplasia All bone marrow elements showed some hypoplasia when nonprotein nitrogen rose above 150 mg but erythroid tissue was selectively more affected than other cells Aplastic normoblastic tissue was never observed in these marrows

Discrepancy between anemia in peripheral blood and the apparent adequacy of erythroid tissue in bone marrow in many cases of chronic glomerulonephritis is difficult to explain Apparently the mechanism regulating delivery of cells to the blood stream is at fault rather than the maturation of cells This mechanism is a selective one since there is no interference with leukopoiesis and megakaryopoiesis The authors emphasize that a cellular bone marrow in chronic glomerulonephritis is not in itself evidence of hemopoietic activity nor does it have prognostic significance

Chronic Marrow Failure Myelosclerosis and Extramedullary Hematopoiesis When a case was reported 70 years ago of generalized osteosclerosis with striking hepatosplenomegaly anemia hyperplastic lymph nodes and extreme leukocytosis a controversy began over the nature of this condition which still continues Such clinical pictures are infrequent and

stromal cells and clinical abnormalities develop because of inadequate organ function progressing to organ failure and death In chronic marrow failure five major etiologic groups have been identified extrinsic toxic agents liver dysfunction endocrine disease chronic hemorrhage or hemolysis and cardiovascular disease

The authors developed a working hypothesis of the pathogenesis of chronic marrow failure and myelosclerosis Benzene and related aromatic compounds are metabolized by oxidation to phenol catechol and hydroquinone which normally are rapidly conjugated in the liver to sulfates and glucuronates and excreted in urine Adrenal cortical and estrogenic steroids which possess phenolic or quinone groups are similarly conjugated and excreted by the liver in bile and urine These substances are toxic to the lipoid containing partly mature hemopoietic cells Studies of liver conjugation have shown that coenzyme I is necessary for inactivation of estrogenic phenolic compounds In chronic marrow failure pellagra hemochromatosis and copper poisoning suspicion has been directed toward deficient or inactivated coenzyme I as a basic biochemical lesion Hydroquinone and radiation have been suggested as mitotic poisons which also inhibit other unidentified enzymes

[This is a thoughtful discussion of a complex condition of slow evolution pre enting various clinical and pathologic a pects at different stages —Ed]

Hemopoietic Changes during Administration of Chloramphenicol (Chloromycetin®) were observed by Italo F Volini Irving Greenspan Lee Ehrlich James A Gonner Oscar Felsenfeld and Steven O Schwartz[1] (Cook County Hosp) A Negro boy aged 11 with uncomplicated typhoid had a red cell count of 850 000 and 17 per cent (2 6 Gm) hemoglobin four days after discontinuance of therapy He had received a total dose of 53 Gm chloramphenicol orally in 18 days Two other cases were observed almost simultaneously a patient with typhoid complicated by amebiasis had been given 53 Gm chloramphenicol in 19 days and a patient with brucellosis had received 26 Gm in 9 days

There was a precipitous fall in total leukocyte count which occurred by the seventh day in one case and continued

(1) J A M A 142 1333 1335 Ap 29 1950

of leukemic and other neoplastic cells was acquired only exceptionally Histories and laboratory data often incomplete pointed to the etiologic importance of the same agents as those in refractory anemia It is important to differentiate this disease from myelogenous leukemia because the usual therapy for leukemia and splenectomy are contraindicated Splenic hepatic and other extraosseus foci of hemopoietic cells in such patients are attributed to the impossibility of compensatory assumption of blood formation in diseased bone marrow by viscera which had actively formed blood cells during embryonic life It is generally agreed that myelocytes and nucleated red cells in peripheral blood are not certain indicators of myelogenous leukemia

The gross appearance of organs at autopsy will suggest this condition Spleen is 3 30 times larger than normal Fibrosis is at times indicated by resistance to cutting In some cases infarcts are present and there may be dark red or brown spherical demarcated nodules of bulging soft tissue Liver is 1½-4 times its usual weight but on section does not appear abnormal The marrow may be deep red and succulent displacing the usually intermingled yellow fat and appearing grossly hyperplastic Bones may be uniformly dense gray white and hard with thickened cortices and without well defined marrow spaces

In the literature consulted 129 adequately studied acceptable cases of this morphologic entity were found Natural life span in chronic marrow failure and myelosclerosis usually extends over many years although the patient may not appear for examination until late in its course Search often uncovers evidence of toxic exposure Complete hematologic investigation including bone marrow biopsy (not puncture) is indicated Methods useful in treatment of leukemia and hypersplenism are contraindicated Splenectomy usually shortens the patient s life

Bone marrow has been compared in size with the liver and pathologic analogies may be drawn between myelosclerosis and hepatic cirrhosis Both are morphologic entities without etiologic unity In both diseases various toxic agents deficiencies and injuries cause necrosis of parenchyma followed by reparative hyperplasia of surviving cells Continuance of parenchymal damage leads to overgrowth of the tougher

stromal cells and clinical abnormalities develop because of inadequate organ function progressing to organ failure and death In chronic marrow failure five major etiologic groups have been identified extrinsic toxic agents liver dysfunction endocrine disease chronic hemorrhage or hemolysis and cardiovascular disease

The authors developed a working hypothesis of the pathogenesis of chronic marrow failure and myelosclerosis Benzene and related aromatic compounds are metabolized by oxidation to phenol catechol and hydroquinone which normally are rapidly conjugated in the liver to sulfates and glucuronates and excreted in urine Adrenal cortical and estrogenic steroids which possess phenolic or quinone groups are similarly conjugated and excreted by the liver in bile and urine These substances are toxic to the lipoid containing partly mature hemopoietic cells Studies of liver conjugation have shown that coenzyme I is necessary for inactivation of estrogenic phenolic compounds In chronic marrow failure pellagra hemochromatosis and copper poisoning suspicion has been directed toward deficient or inactivated coenzyme I as a basic biochemical lesion Hydroquinone and radiation have been suggested as mitotic poisons which also inhibit other unidentified enzymes

[This is a thoughtful discussion of a complex condition of slow evolution presenting various clinical and pathologic aspects at different stages —Ed]

Hemopoietic Changes during *Administration* of Chloramphenicol (Chloromycetin®) were observed by Italo F Volini Irving Greenspan Lee Ehrlich James A Gonner Oscar Felsenfeld and Steven O Schwartz[1] (Cook County Hosp) A Negro boy aged 11 with uncomplicated typhoid had a red cell count of 850 000 and 17 per cent (2 6 Gm) hemoglobin four days after discontinuance of therapy He had received a total dose of 53 Gm chloramphenicol orally in 18 days Two other cases were observed almost simultaneously a patient with typhoid complicated by amebiasis had been given 53 Gm chloramphenicol in 19 days and a patient with brucellosis had received 26 Gm in 9 days

There was a precipitous fall in total leukocyte count which occurred by the seventh day in one case and continued

(1) J A M A 142 1333 1335 Ap 29 1950

as long as the drug was administered Leukopenia resulted primarily from a decrease in marrow granulocytes due to a maturation arrest without significant alteration in monocytes or lymphocytes Severe anemia occurred in one patient with an erythroid maturation arrest in marrow No significant change occurred in platelet count in the one instance in which this factor was studied Both marrow and blood changes were reversible and an immediate rise in white cell count followed discontinuation of therapy

Although pronounced hematologic changes have been reported to accompany typhoid and no toxic effects have previously been ascribed to orally given chloramphenicol the following evidence strongly suggests the cause and effect relationship between administration of the drug and marrow and blood changes Leukopenia developed after chloramphenicol therapy was started despite definite clinical improvement Absolute and relative granulocyte levels uniformly fell lower than those ordinarily observed in typhoid or brucellosis In every instance marrow showed a relative and absolute granulopenia with maturation arrest An immediate precipitous increase in granulocytes and leukocytes followed discontinuance of chloramphenicol therapy On the basis of erythroid maturation arrest chloramphenicol was probably partly responsible for the decrease in red cells

The authors conclude that toxic manifestations of this drug will have to be studied more extensively before it can be considered an absolutely safe therapeutic agent

↓ In the following two articles the effects of cobalt administration in man are discussed Though essential as a trace element in hemopoiesis it does not appear to have useful effects in pharmacologic dosage in the treatment of anemia —Ed

Effect of Oral Therapy with Cobaltous Chloride on Blood of Patients Suffering with Chronic Suppurative Infection Joseph C Robinson G Watson James III and Robert M Kark (Chicago) studied the blood of nine patients aged 18 36 with prolonged suppurative infections treated for 2 11 weeks with 20 60 mg cobaltous chloride daily by mouth The patients had already been hospitalized an average of 26 months for chronic osteomyelitis or chronic soft tissue suppuration They showed no clinical evidence of vitamin or pro

( ) N w E gl d J M d 240 749 753 M y 12 1949

tein deficiencies although all had lost weight Red cell sedimentation rate was increased plasma iron levels were low and plasma copper levels were increased in all Before treatment red cell counts reticulocyte counts hemoglobin concentrations *hematocrit levels and total circulating* hemoglobin were constant and reduced below levels found in bedridden control subjects Total circulating hemoglobin levels were

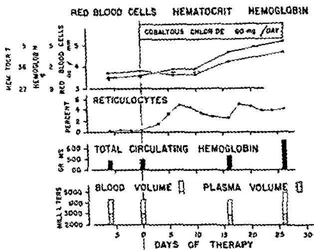


Fig 76—Eff t f b lt hl d blood f s th 19 w th h t t d 1 my l t (C t y f R b J C s / \ w E gl d J M d 40 749 753 M y 12 1949)

significantly reduced on the average of 26 per cent below values for controls

After treatment reticulocyte responses occurred in all patients as early as the fourth day and continued throughout therapy Maximal reticulocyte percentages were usually observed between 6 and 10 days and did not exceed 5 per cent A typical reticulocyte response is shown in Figure 76 In this patient as in the others a steady increase in red cell counts hematocrit levels and total circulating hemoglobin followed the reticulocyte response On the average blood values of all patients reached normal levels after cobalt therapy There was a significant change in blood volume owing mainly to a 30 per cent increase in circulating red cell mass

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(2) New E gl d J M d 240 749 753 M y 1 1949

studied the erythropoietic effect of cobalt first in hematologically normal patients then in patients with anemias refractory to recognized forms of treatment A 2 5 per cent aqueous solution of cobaltous chloride was given to 61 patients Generally 4 cc containing 100 mg cobaltous chloride was given orally three times daily after meals

Daily oral administration of 300 mg cobaltous chloride to 17 patients without anemia produced slight reticulocyte re

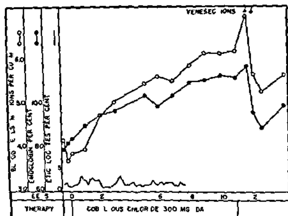


Fig 77 —Results of cobalt administration in a man with generalized osteoporosis and osteoarthritis (Courtesy of ... New England J Med 240 754 761 May 1949)

sponses in all within a week All but 1 of the 10 given the drug for over four weeks showed moderate increases in red blood cell hemoglobin and hematocrit values A man 67 with severe generalized osteoporosis and osteoarthritis was given the drug for 11 weeks with striking effects on red cell and hemoglobin levels (Fig 77) After 10 weeks of treatment he complained of poor appetite and sensations of fulness in the head Cobalt administration was stopped a week later and five days thereafter at the height of polycythemia 500 cc blood was removed on two successive days The red cells contained spectrophotometrically normal oxyhemoglobin and survived normally when transfused into another patient

Similar doses were given 32 patients with various types of anemia refractory to other forms of therapy 20 being

the plasma volume changing but slightly Total circulating hemoglobin increased on the average 29 per cent above pretreatment levels In four patients on whom measurements were made before and after treatment plasma iron and copper levels were not affected by therapy Two patients had slight loss of appetite All showed a dusky skin discoloration especially pronounced below the eyelids It was probably due to the dye T 1824 used for measuring blood volumes but may have been an effect of cobalt No other abnormal signs or symptoms were observed

Hemopoietic responses to cobaltous chloride indicate that the drug produced an active stimulus to erythropoiesis since a distinct reticulocytosis preceded a rise in erythrocyte count. Mode of action of cobalt on blood remains a mystery It does not seem possible that cobalt has a specific effect on the blood of patients with chronic infections Their anemia is refractory to liver therapy and they require relatively large quantities of cobalt for erythropoiesis to occur Hemopoiesis after massive cobalt therapy is more likely due to a nonspecific stimulus to bone marrow

Erythropoietic Effect of Cobalt in Patients with or without Anemia Cobalt in the form of one of its salts usually cobaltous chloride or nitrate has been shown to produce polycythemia in amphibia birds and mammals Since pioneer observations in 1929 metallic cobalt or its salts have been given to animals and man in efforts to combat anemia produced by disease It has been reported that cobaltous nitrate counteracts the inhibitory effect on erythropoiesis of benzene administration in rabbits and that cobalt administration abolishes anemia or even produces polycythemia in rats with sterile inflammation produced by intramuscular injection of turpentine Only a few results briefly documented have been reported from use of cobalt salts as a stimulus to erythropoiesis in human disease However almost at the time the present investigation was begun a report in the German literature indicated that oral administration of 500 mg cobaltous chloride daily regularly produced reticulocyte responses in normal subjects and thereafter increases in red cell hemoglobin and hematocrit values

Lionel Berk Joseph H Burchenal and William B Castle[3]

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(3) N w E gla d J M d 40 754 61 M y 12 1949

HYPERSPLENISM

The use of this term with its implications has the sanction of several authorities They conceive the existence of hematologic conditions usually *associated with splenomegaly to result from an exaggerated function* of the spleen For this reason a few articles have been segregated in this section. However we doubt that the concept of primary hyperfunction of the spleen can be supported, despite the fact that splenectomy is frequently a useful procedure. Rather it appears to us that, owing to a variety of causes originating external to the spleen the organ may become secondarily enlarged and its function increased. The very number of recognizable causes of secondary splenomegaly associated with anemia, leukopenia and thrombocytopenia or sometimes with only one of these suggests this interpretation Thus in congenital hemolytic jaundice the red cell defect is clearly primary and persists after splenectomy With congestive splenomegaly of origin internal or external to the liver or a spleen enlarged by infiltration by Gaucher's cells leukopenia and thrombocytopenia *are common In various instances of acquired hemolytic* jaundice agglutination of the red cells sometimes augmented by slight lowering of the pH of the serum is observed. If the normal spleen as can easily be shown is able selectively to retain pheroidal red cells it should even more readily sequester red cells that are agglutinated

Even among those convinced of the primary nature of the process both hyperphagocytosis in the spleen and hypofunction on the part of the marrow as a result of undetermined splenic humoral influences are proposed as explanations Consequently there is no general agreement as to the definitive diagnostic criteria of hypersplenism As splenomegaly with anemia leukopenia and thrombocytopenia are common to such diverse conditions as for example refractory anemia with hyperplastic bone marrow aleukemic myelogenous leukemia and disseminated lupus the *diagnosis of hypersplenism is possible only in retrospect when splenectomy* effects a change toward normal in the blood picture In our limited experience this can happen only when manifest leukemia develops months or even years later In a later section articles on chronic sometimes cyclic, agranulocytosis are assembled The varied morphology of the bone marrow and the indifferent effects of splenectomy are to be noted This does not deny the utility of splenectomy in certain patients it only suggests the uncertainty of the concept of hypersplenism as a primary aberration of the spleen —Ed

Problem of Hypersplenism is summarized by Roy R Kracke and William H Riser Jr[4] (Birmingham Ala) Functional overactivity of the spleen (hypersplenism) includes a variety of hematologic syndromes with multiple clinical pictures in which the spleen has the capacity to destroy various blood cells Such syndromes include chronic and acute splenic neutropenia chronic and acute splenic panhematopenia of congenital and acquired types familial hemolytic icterus and idiopathic thrombopenic purpura

(4) J A M A 141 113 1139 D 17 1949

treated over four weeks Two of five with moderate anemia associated with chronic infections one of two with hypo chromic anemia associated with inoperable gastric carcinoma and one with familial microcytic (Cooley s trait) anemia showed definite reticulocyte responses and rises in red cell hemoglobin and hematocrit values

Only 3 of 16 patients in the lymphoma group—2 with reticulum cell sarcoma and 1 with chronic lymphatic leu kemia—showed even suggestive evidence of ability to main tain higher erythrocyte and hemoglobin levels In none of five patients with refractory anemia and hypercellular bone marrow was erythropoiesis detectably affected One patient with anemia of hepatic cirrhosis showed no response in an adequate trial Two patients with anemia associated with chronic renal failure given the drug for only a few days showed no evidence of a reticulocyte response

From these observations it seems clear that cobaltous chloride increases erythropoiesis in hematologically normal subjects Reticulocyte responses resembled in chronology those resulting from hemorrhage anoxia or iron or liver ex tract administration under circumstances appropriate to each This observation is seemingly consistent with the possibility that cobalt interferes with transport of oxygen in erythroid cells of the bone marrow because of its ability to form oxygen binding complexes with certain amino acids such as cysteine and histidine If so the agent would be expected to be effec tive in elevating the hemoglobin level in patients with little or no anemia rather than in those with severe anemia in whom a powerful anoxic stimulus to erythropoiesis presum ably already exists

There is little evidence of toxicity of cobalt at least after oral administration other than irritation of the alimentary tract However there is also little probability of benefit in severe types of anemia otherwise unamenable to therapy In mild anemias associated with chronic infections benefit due to a slight increase in hemoglobin may well be offset by loss of appetite due to the drug Therefore clinical use of cobalt should be limited to cases of anemia in which other methods of treatment are clearly of no value There is no indication for use of cobalt as an adjuvant to liver or iron therapy

pleted cell values in blood including neutropenia thrombo penia anemia or various combinations of these demonstration of unimpaired bone marrow production and demonstration of splenic overactivity by the epinephrine test The basic problem in hypersplenism is to determine whether or not the spleen is destroying more cells than it should and whether or not the bone marrow is capable of producing the normal number of cells to support the particular patient then the danger of leaving the spleen in the patient can be weighed against the operative risk of removing it Splenectomy is always a serious surgical procedure and should be carried out only by a competent surgeon

Primary Splenic Panhematopenia The term splenic pan hematopenia is used to designate a syndrome characterized principally by splenomegaly panhyperplasia of the bone marrow and varying degrees of anemia neutropenia and thrombocytopenia The syndrome is divided into primary splenic panhematopenia on a congenital or familial basis and splenic panhematopenia secondary to some constitutional pathologic process with disturbed splenic physiology The primary type of splenic panhematopenia may occur as a chronic relapsing disease with intermittent episodes of hemoclastic activity or as a relatively acute disease characterized by prostration and rapid depression of the cellular elements of the blood The secondary acquired form of panhematopenia has been observed in Hodgkin s and Gaucher s diseases

Based principally on results of epinephrine tests supravitally stained preparations of freshly excised splenic tissue and histologic appearance of the bone marrow it has been thought that the hematologic alterations in splenic panhematopenia are due to sequestration of erythrocytes leukocytes and thrombocytes in the splenic sinusoids and destruction of these elements by reticuloendothelial macrophages In most cases reported subcutaneous administration of 0 5 1 cc epinephrine produced significant elevation of number of circulating erythrocytes leukocytes and thrombocytes

During the past few years Robert W Heinle and William D Holden[5] (Cleveland) have diagnosed primary splenic pan hematopenia in seven instances The patients presented the picture described in primary splenic panhematopenia Neu

(5) S g Gynec & Ob t 89 79 91 J ly 1949

The spleen is the most important organ in the body with respect to cellular destruction Histologic evidence can be seen in the large endothelial cells which show fragments of red and white cells and thrombocytes incorporated in the cytoplasmic structure Furthermore motion pictures of the splenic pulp clearly show the active process of phagocytosis by the ameboid endothelial elements of the spleen Examination of the venous blood supply shows a definite increase of bilirubin in the splenic vein compared with the splenic artery Other evidence of cellular destruction is found in large deposits of hemosiderin the iron containing pigment of disintegrated red cells

In addition to removing cellular elements from blood by phagocytosis and ultimate destruction the spleen is also capable of removing large masses of cells from the vascular system by enlargement and sequestration of the cells in the dilated and engorged organ Therefore it is a reservoir the chief function being to store blood however this function may become perverted and excessive numbers of cells removed from the vascular system resulting in depleted cellular values in peripheral blood This storing of large quantities of cells can be amply demonstrated by the epinephrine test An injection of 0 5 1 cc of 1 1 000 epinephrine solution will cause contraction of the organ and a simultaneous rise in cellular value in peripheral blood

Most circulating blood cells are produced in bone marrow which has a tremendous reserve capacity for producing blood cells The relation of marrow production and splenic destruction may be summarized as follows normal marrow production plus normal splenic destruction produces normal cellular equilibrium impaired production plus normal destruction causes depleted cellular elements normal production plus excessive destruction causes depleted cellular elements The spleen may be hyperfunctional for many years but if cellular destruction is not too great the marrow may be able to maintain normal cellular values Only when marrow decompensation occurs do signs of anemia thrombopenia and neutropenia develop

Diagnostic criteria for hypersplenism include these cardinal features a spleen clinically enlarged the single exception being some cases of essential thrombopenic purpura de

preponderant and their action results in pathologic conditions It has been stated that excessive hemolysis is due either to normal hemolytic agents acting on defective erythrocytes or to exposure of red blood cells of normal resistance to lytic agents in unusual quantity or of unusual activity Whichever occurs the spleen must play an important role since splenectomy has proved life saving in management of certain hemolytic syndromes Evidence seems to accumulate that the macrophages of the spleen are specifically responsible for the abnormal activity They not only dispose of the effete blood cells by engulfing them but also elaborate various enzymes which prepare the blood cells for destruction

George J Scheff and Ahmed J Awny[6] (Ohio State Univ) studied lecithinase activity in 10 pathologic spleens (9 obtained at operation) and 2 normal spleens obtained at autopsy Patients operated on had typical essential thrombocytopenic purpura splenic neutropenia and congenital hemolytic icterus In all of them the spleen was the major factor in the ailment so that the term hypersplenism was applicable to all In all the pathologic spleens increased lecithinase activity was demonstrated by increased formation of lysolecithin in vitro In the two normal spleens this effect was lacking

Mere demonstration that the reticuloendothelial cells of the spleen are numerically increased and functionally hyperactive in producing the enzyme would not be sufficient to explain the whole picture in hypersplenism These cells are widely distributed in the organism and are not restricted to the spleen alone To explain the key position of the spleen in hemolytic processes the authors emphasize that in the spleen circulation is largely cut off from the main blood flow and therefore blood is permitted to stagnate for various lengths of time Complete separation between cells and plasma is also thought to exist In these circumstances not only is the lecithinase activity enhanced in hypersplenism owing to the increased number of macrophages in the spleen but simultaneously the inhibitory effect of plasma is reduced to a minimum In addition a more intimate contact between blood cells retained in meshwork of the pulp and the freshly elaborated lysolecithin can be established This may gradually lead to spherocytosis and to sensitization of the erythrocytes for

(6) Am J Cl P th 19 615-620 J ly 1949

tropenia anemia and thrombocytopenia occurred in all and varied from mild to severe Splenomegaly was constantly present but variable in degree Purpura was observed depending on degree of thrombocytopenia Oral ulcerations were present in one patient and chronic ulcers on the legs of another both of whom had severe and presumably chronic neutropenia Mild jaundice occurred in only one of the seven patients Bone marrow was hyperplastic in all

All the patients were subjected to splenectomy One patient died after operation The others were markedly improved but hematologic improvement tended to be gradual and prolonged rather than immediate and complete Examination of the spleen did not reveal any other disease that might have accounted for the hematologic disturbance The histologic picture was not characteristic or specific and generally no more than mild follicular hyperplasia could be demonstrated Failure to demonstrate excessive phagocytosis in spleens of these patients makes it doubtful that phagocytosis is the mechanism responsible for production of primary splenic panhematopenia Nor in the authors experience was the epinephrine test helpful in diagnosis or interpretation of the mechanism of this syndrome The rise in leukocyte count following administration of epinephrine results from appearance of increased numbers of lymphocytes in peripheral blood with little change in number of polymorphonuclear neutrophils

Role of the spleen in splenic panhematopenia is therefore not clearly defined especially when patients with this syndrome continue to show no excessive phagocytosis The authors suggest an alternative explanation namely that the spleen has a regulatory effect on bone marrow The anemia not clearly hemolytic may be the result of failure of proper discharge of erythrocytes from the marrow Presence of neutropenia and thrombocytopenia could be explained likewise on the basis of suppression of discharge of these elements from the marrow

Lecithinase Activity in Splenic Dyscrasias Mechanism of red blood cell destruction in vivo is extremely complex and only incompletely understood Though phagocytosis and fragmentation may sufficiently explain normal destruction of blood corpuscles in certain anemias the lytic factors become

eight clinical remission in the remaining eight was maintained despite hematologic relapse

When the spleen is enlarged from any cause leukopenia thrombopenia and anemia may occur this is the syndrome of hypersplenism Primary splenic disorder in which no associated disease is demonstrated is called primary hypersplenism Secondary hypersplenism occurs in many conditions perhaps the commonest is congestive splenomegaly of portal hypertension Splenectomy was performed on 10 patients with hypersplenism secondary to splenic or portal vein block cirrhosis or Gaucher s disease and on 1 patient with primary hypersplenism Normal blood levels were maintained after surgery in the 10 with secondary hypersplenism The patient with primary hypersplenism showed improvement for about three months when leukopenia recurred

Indications and Results of Splenectomy are discussed by Warren H Cole Leroy Walter and Louis R Limarzi[8] (Univ of Illinois) Data presented were obtained from study of 87 patients who had had splenectomy in the past 12 years

Results of splenectomy are best in hemolytic jaundice and thrombocytopenic purpura but even in these diseases extreme care must be exercised in selecting the patient Close cooperation between surgeon and hematologist is essential since the indications for splenectomy can rarely be classified as positive unless results of a sternal puncture as interpreted by a skilled hematologist are known

It is frequently very difficult to differentiate congenital hemolytic jaundice in which splenectomy is almost universally successful from acquired hemolytic jaundice in which poor results are common [Differential diagnosis is not difficult with modern methods demonstration of increased osmotic fragility of the red cells in members of the family in congenital hemolytic jaundice and specific tests such as Coombs cold agglutinin acid hemolysin etc for acquired types — Ed] Anemia in the former condition is microcytic and in the latter macrocytic In many patients with acquired anemia there is no increase in red cell fragility In 28 patients with hemolytic anemia in the authors series results were good to excellent in 23 with the congenital type but were good in only 1 of 5 with acquired hemolytic anemia

(8) A S g 129 702 723 M y 1949

hemolysis After splenectomy the spherocytosis may persist because of continued formation of lysolecithin in other parts of the body but in absence of the spleen the principal site of destruction is eliminated The fundamental difference in action of lysolecithin in stagnant and circulating blood is the best explanation for its striking action in the hyperactive spleen

Medical Aspects of Splenectomy H N Robson[7] (Univ of Edinburgh) states that splenectomy is of value in hemolytic disease in hemorrhagic disease due to thrombopenia and in hemocytopenia or reduction in blood cells occurring in the presence of an enlarged spleen In none of these groups is it known whether the blood changes are caused by remote influence of the spleen on the bone marrow or by local destruction of blood cells within the spleen

Of the many forms of hemolytic disease splenectomy is most consistently successful in familial hemolytic anemia In other forms of familial hemolytic disease such as Cooley s and sickle cell anemia splenectomy is rarely successful In acquired idiopathic hemolytic anemia results are variable in the acute and subacute forms splenectomy should be considered when repeated blood transfusions have failed to produce remission and in the chronic form when there are recurrent crises incapacitating anemia or formation of gallstones Acquired symptomatic hemolytic anemia in patients with reticulosis lipoidosis sarcoidosis tuberculosis and leukemia may respond to splenectomy In 13 patients with hemolytic anemia results of splenectomy were good in 4 with familial hemolytic anemia in 5 of 7 with the chronic form of acquired idiopathic hemolytic anemia and in 2 with the acute form of this disease

Splenectomy is of value in hemorrhagic disease only when thrombopenia is present Splenectomy is usually contraindicated in thrombopenia secondary to bone marrow disease though success was reported in a case of gold toxicity It is principally indicated in idiopathic thrombopenia Of 19 patients with idiopathic thrombopenic purpura treated with splenectomy complete clinical remission was produced in 16 These patients were observed for periods of 6 months to 17 years after operation Bleeding time capillary fragility and platelet counts were maintained at fully normal levels in

(7) Edinburgh M J 56 381 395 September 1949

POLYCYTHEMIA

The cause of this disease continues to attract speculation and to defy demonstration To the well known association with myelogenous leukemia recorded by Merskey Lawrence now adds four cases of multiple myeloma and an excellent account of his experiences with radioactive phosphorus in the treatment of the disease —Ed

Oxygen Saturation of Sternal Marrow Blood in Polycythemia Vera Observation of polycythemia at high altitudes and in certain forms of pulmonary and congenital heart disease has led to acceptance of the view that anoxia is an erythropoietic stimulus *In polycythemia vera however oxygen* saturation of arterial blood is normal Observers have therefore sought in bone marrow itself the evidence of anoxia in this disease Changes in capillaries and arterioles in bone marrow of patients with polycythemia vera have been demonstrated and decreased blood flow with subsequent anoxia as the erythropoietic stimulus has been postulated Chemical evidence of such anoxia has not been obtained however It has likewise been maintained that marrow anoxia is the stimulus to red cell production in anemia as for example after hemorrhage However studies of the percentage saturation and oxygen tension of bone marrow blood in dogs made anemic by bleeding have revealed no significant difference from the values in control animals These considerations led Bernard M Schwartz and Daniel Stats[9] (Mount Sinai Hosp New York City) to a study of the oxygen content in bone marrow blood in various disorders in man

Studies were done on 50 patients divided into four groups namely controls and patients with polycythemia vera anemia and anoxic anoxia From each patient within a period of several minutes specimens of bone marrow blood and brachial arterial blood were obtained Oxygen determinations were performed by the method of Roughton and Scholander

Results showed that percentage saturation of bone marrow blood was greater and the arterial bone marrow blood oxygen difference was smaller in patients with polycythemia vera than in controls This finding does not support the theory that there is local bone marrow anoxia due to decreased

(9) J Cl I ig ton 28 736 740 J ly 1949

Although results are good in fully 90 per cent of patients having splenectomy for thrombocytopenic purpura they are rarely good in secondary or symptomatic purpura Best means of differentiating these two conditions is by bone marrow studies A marked increase in megakaryocytes is indicative of thrombocytopenic purpura this feature is of great prognostic value In 23 of 26 patients having splenectomy for thrombocytopenic purpura results were good to excellent and in the other 3 fair to good

The authors encountered 13 patients with what they classified as Banti s disease and 5 in whom they considered obstruction (anomalous or thrombotic) of the splenic vein to be the primary cause of the splenomegaly and portal hypertension Of the 13 patients with Banti s disease 5 died after splenectomy and in only 2 were results good In contrast four of five patients with obstruction of the splenic vein had good results from splenectomy The fifth patient still has occasional hemorrhages from esophageal varices and a portacaval shunt is contemplated Because results are so different the authors prefer to separate the two groups mentioned rather than classify them all as portal hypertension The authors are convinced that splenectomy should be performed in Banti s disease only in its early stages

Good results were obtained in four of five patients with Felty s disease which may also be classified as secondary panhemocytopenia although there was little improvement in arthritis There were no patients with primary splenic neutropenia or panhemocytopenia

Among the 87 patients there were 7 operative deaths 5 of which occurred in Banti s disease The authors recommend that careful study be made in this disease and splenectomy not be performed if hepatic insufficiency or other significant complications are present

[Moreover as emphasized in the discussion of this paper splenomegaly in this group of conditions is the result of splenic vein hypertension usually in turn a reflection of portal hypertension itself a sequel of cirrhosis At operation the point of obstruction must be located if possible If in the liver the splenic vein offers the best hope of a successful anastomosis to the left renal vein If splenectomy alone is performed little if any relief of portal hypertension will result and the splenic vein will not be available at a subsequent operation For this reason no surgeon unfamiliar with vascular anastomotic surgery should undertake to enter the abdomen with the objective of splenectomy in these patients —Ed.]

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(9) J Cl I t g t on 8 736-740 J ly 1949

blood flow in polycythemia vera but is compatible with either increase in blood flow or decrease in oxygen utilization by the marrow in this disease No significant differences were found between the values in anemic patients and those in controls In patients with anoxic anoxia due to chronic pulmonary disease or to right to left shunts in the heart some of whom were polycythemic the percentage saturation of bone marrow blood with oxygen was lower than in controls

[In similar observations by Berk and others it was concluded that penetration of the bone marrow cavity by the sampling needle may so disturb conditions of local blood flow as to result in samples of blood not truly representative of the unaltered vascular relationships —Ed]

Relationship between Polycythemia Vera and Myeloid Leukemia Critical Review The exact nature of polycythemia vera (erythremia) is unknown However most theories regarding the fundamental pathology either link erythremia with erythrocytosis using anoxemia as a common denominator or consider the disease closely allied to myeloid leukemia

Clarence Merskey[1] (Univ of Cape Town) reviewed most reported cases in which a relationship between erythremia and myeloid leukemia was thought to have existed Leukemia was considered the diagnosis only if leukemic infiltrations outside bone marrow were proved at autopsy However such a minimal requirement for the diagnosis of leukemia was not always applicable Particularly the group of diseases known variously as chronic nonleukemic myelosis myeloid megakaryocytic splenomegaly and agnogenic myeloid hyperplasia required special consideration Leukocytosis was found to occur in erythremia and occasionally considerable myeloid hyperactivity was found In many of these patients the type of therapy used could have been the cause of excessive leukoblastic activity when it occurred Only two cases of erythremia were found in which no material therapy was used and in which the diagnosis was acceptable however one was associated with myelofibrosis and in the other the diagnosis could not be considered conclusive because there was no autopsy In nine cases the diagnosis of erythremia was acceptable but the patients had received some form of therapy only four were followed to autopsy and not all could definitely be considered to have had myeloid leukemia also In most cases the presence of all features necessary to state definitely that the

(1) Clin Proc 8 150 162 September 1949

two conditions are related was not proved conclusively this was also true in cases of acute leukemia supervening in erythremia It is concluded that whereas some degree of myeloid hyperactivity is usually present in many cases of erythremia and in certain ones it may produce a leukemoid blood picture true erythremia associated with true leukemia is rare

In these cases anemia was not always present but there usually were primitive red and white cells in peripheral blood generally without the high number of leukocytes characteristic of leukemia There was a large spleen At autopsy foci of extramedullary erythropoiesis and leukopoiesis sometimes were found throughout the spleen and liver and occasionally in the kidney and lymph nodes Similar findings were associated with myelofibrosis and myelosclerosis It was not possible to know how frequently osteosclerosis or fibrosis occurred in patients with nonleukemic myelosis because the results of x ray examination of the skeleton were rarely recorded and fibrotic changes in bone marrow could only be detected by complete postmortem examination of the skeleton Patients with massive myeloid splenomegaly and osteosclerosis showed the same variations in duration of disease and in type of blood picture as patients with myeloid splenomegaly without osteosclerosis In both groups there were acute and chronic cases immature cells were usually present in circulating blood and blood studies sometimes showed a great increase in circulating leukocytes a high proportion of which sometimes were immature

On the basis of these cases it seems likely that erythremia can result in myelofibrosis or myelosclerosis If it can be concluded that this syndrome is essentially leukemia then erythremia and myeloid leukemia are certainly related It has been suggested that leukoerythroblastosis and myelofibrosis or myelosclerosis might occur simultaneously in response to a single but unidentified stimulus since all the cell types involved namely the osteoblast fibroblast hemocytoblast and megakaryocyte are derived from the same primitive mesenchymal reticular cell of Maximow Therefore it is possible that excessive hyperplasia of the totipotential cell involves all the blood elements (erythremia) predominantly affects myeloid elements along normal lines (nonleukemic myelosis) or goes on to uncontrolled proliferation (myeloid leu

kemia) On this basis it is easy to see how such a powerful therapeutic agent as irradiation could upset an already disturbed hemopoietic apparatus and predispose a patient to development of leukemia or anemia

Multiple Myeloma Associated with Polycythemia Report of Four Cases Simultaneous development of myeloma and polycythemia vera in one patient is of interest for a number of reasons Both conditions chiefly involve bone marrow Their etiology is unknown and their simultaneous appearance is rare Review of the literature reveals three reports of polycythemia vera associated with possible myeloma John H Lawrence and Robert L Rosenthal[2] (Univ of California) report four cases of definite myeloma associated with polycythemia The patients were first studied and followed because of polycythemia Myeloma was an unexpected development or finding

CASE 1—Man 59 had symptoms and a blood picture consistent with diagnosis of polycythemia vera No symptomatic improvement followed treatment with radioactive phosphorus although red cell count fell to normal after administration of 35 33 mc in seven months Two years after discovery of polycythemia the patient presented symptoms due to a destructive lesion of the ninth dorsal vertebra He died one year later and at autopsy the lesion was found to be a myeloma composed predominantly of plasma cells.

CASE 2—Woman 50 was found to have polycythemia while living at a high altitude It disappeared when she was at sea level. She complained of pains in the arms and legs and was found to have Bence Jones proteinuria Diagnosis of myeloma was established by discovery of 9 6 per cent plasma cells in aspirated sternal marrow At the time of this report she had been relatively asymptomatic for almost one year

CASE 3—Woman 65 had symptoms suggestive of polycythemia vera of eight months duration Although the red cell count was not significantly elevated an elevated hematocrit reading history and florid appearance were strongly indicative of this disease Bone marrow study revealed 13 per cent plasma cells and x ray examination showed two areas of bone rarefaction

CASE 4—Man 56 had known polycythemia vera for two years He had a brief terminal illness marked by renal failure Autopsy revealed multiple myeloma.

The authors speculate on the part played by myeloma in causing or contributing to polycythemia in each of these cases It is possible that proliferating cells of both the red cell and the myeloma series originate from the same stem

(2) Am. J M Sc. 218 149 154 A gu t 1949

cell with certain unknown factors determining the type of cell produced In these cases the stem cell may first have differentiated into the red cell series to cause the elevated red cell count which later decreased when the stem cell differentiated into myeloma cells

Since these patients were studied initially for polycythemia unexpected discovery of myeloma provides some information about the course of the latter disease In Case 2 there have been no symptoms which could be definitely attributed to myeloma for one year since its discovery It is evident that myeloma can be present in a latent state Little is known about this latent state and its duration

Whether radioactive phosphorus given in Case 1 could have been a factor in causing myeloma cannot be answered but it is unlikely that such small doses could induce neoplasm so soon after radiation therapy

Control of Polycythemia by Marrow Inhibition Ten Year Study of 172 Patients with polycythemia from various causes is reported by John H Lawrence[3] (Univ of California) There was no clearcut differentiation between primary and secondary polycythemia although most patients with the primary disease presented the classic picture and most of those with the secondary form had an obvious cause for the elevated red cell count However there were patients in between these classifications in whom the question of anoxia arose This led *to a consideration of whether an anoxic stimulus may not be* a factor in all cases of polycythemia

Radioactive phosphorus (P^{32}) was given 121 patients with polycythemia vera aged 19 75 at time of onset (average 50 7) and follow up studies were made to evaluate this form of therapy with reference to life expectancy or prolongation of life Palpably enlarged spleens were present in 65 per cent After therapy the spleens became smaller White blood cell counts above 10 000 were noted in 68 per cent initially and of these 38 per cent had myelocytes or immature white cells This finding is of interest because of the relation between polycythemia vera and leukemia and the frequent occurrence of leukemia as a complication of polycythemia vera Of those having immature white cells 69 per cent had received previous therapy After P^{32} therapy immature white cells were

(3) J A M A 141 13 18 Sept 3 1949

found in only 27 per cent of those originally having such cells About 4 per cent of the total series had myelocytes in the peripheral blood after P^3 therapy but not before No patient with a normal total white cell count initially had myelocytes in the peripheral blood A third of the patients had elevated blood pressures and a third of these showed a fall in pressure after P^{32} therapy There was peptic ulcer or a history of it in 11 5 per cent and a history of thrombosis in 14 8 per cent

When necessary arterial blood oxygen saturation studies were done to rule out secondary polycythemia as were special pulmonary and cardiac studies Criterion for diagnosis was a red blood cell count of 7 000 000 or over unless there was clearcut evidence of the diagnosis in the past or an enlarged spleen with a definitely elevated red cell count In borderline cases the red cell mass as determined by P^{32} labeled cells and measurement of red cell production with Fe^{59} were often helpful in diagnosis

During 1939–42 30 patients were treated Since that time this group has received one course (usually two injections of 3 6 mc) on the average of every three years Of the 121 patients 47 8 per cent received only one course of therapy Of the first 30 patients 17 per cent remained normal (at the time of this report) for over three years after the single course of therapy Of the group treated during the first five years of the study 28 per cent had only one course of therapy some of them did not need retreatment after four to eight years

There have been 21 deaths causes being generalized arteriosclerosis (5) leukemia (5) neoplastic disease (3) coronary occlusion (3) cardiac failure (2) portal thrombosis (1) anemia and leukopenia (1) and cerebral thrombosis (1) Average age at death was 67

Since four of the five patients who died of leukemia showed some suggestion of it when first seen there appears to be no significant increase in the incidence of this complication after P^{32} therapy Similarly there was no evidence of the consistent occurrence of other complications which might be related to the treatment For example there was no evidence that neoplasms were induced by this therapy Of special interest was the low incidence of thromboses after P^{32} therapy Lawrence concludes that patients with polycythemia vera who are properly treated have as favorable an outlook as do

patients with diabetes mellitus treated with insulin or those with pernicious anemia treated with liver

[This excellent article illustrates the satisfactory remissions that can be obtained in this disease, as here, with P^{32} or by others with spray x radiation —Ed]

LEUKOCYTOSIS AND LEUKOPENIA

Production in Vitro of L E Cell Phenomenon Use of Normal Bone Marrow Elements and Blood Plasma from Patients with Acute Disseminated Lupus Erythematosus is described by Malcolm M Hargraves[4] (Mayo Clinic) A characteristic L E cell (Fig 78) observed in bone marrow of patients with acute disseminated lupus erythematosus was in no case found by direct smear of bone marrow L E cells observed were always in the material outside the touch preparation where the material had come in contact with heparinized plasma Heparin was considered the agent possibly responsible and preparations were made using other anticoagulants including oxalate and citrate The L E cell appeared in all these preparations Consequently venous blood was added to any anticoagulant centrifuged and smears were made from the buffy coat layer in cases in which bone marrow had been positive L E cells were found

A small centrifuge bottle with a narrow intermediate section and expanded portions above and below for use with the venous blood permitted concentration of the buffy coat in a narrow column By this procedure the L E cell has been demonstrated in an occasional case when bone marrow preparations have failed because of the small amount of material obtained The phenomena most commonly observed in material from peripheral blood have been nucleolysis and agglutination in which neutrophilic leukocytes cluster around the rather homogeneous mass of nuclear material and attempt to engulf it

These observations suggested that the material responsible for the nucleolysis agglutination and phagocytosis might be in the plasma of patients with acute disseminated lupus and that it might be possible to produce L E cells by use of bone marrow from patients who did not have the disease Plasma

(4) Proc Staff Meet Mayo Clin 4 234-237 Ap 27 1949



F g 78—a four ne t ph l c polym phonucl a l kocytes (trophl) cl s te d bo t ma f n l m t al d m st at g h m t t eff ct f th f ee, lysed n cl m te al b two L E ells a een in n v t o p p t f blood pl ma f m p t nt w th cute d em nat d l pu ryth matos a d bo e m w eleme t f om p t nt w th n rmal bone m w S m b mat n p tt rn s vi ible n engulf d m t l c two-l bed n t ph l d m t t g cl lys f e of ts lobe d th d tly mut t fig n wh ch th k p me h masome ha unde gone ly and t e ma is bo t to b e gulf d by ph gocyt ne t phil. N te ne t oph l p ud pod e t d g long d f t ll l lea ma e tw n t ph l n t f g lfi g nu l mass N te e of o t ct ndi cati g th t ll h d d d ph gocyt g l g p t n th has th th r The e L E c ll n me fi ld w th wh t p t be tw sep te n l a m sse w th d g t e ol f L E c ll f a oth l mp f thr eu t oph l tt cted t f e nucl a mass In r t l p p rat wh r cti phago yt ca be se n m l cl mp ha b n ob rv d a d wh n o l ko yt ha cd d e g lfi g hem t t e mat al oth r l kocyt s mo e ff nto the fields g l L E ll e d r s lt f n cl ly r h m toly g gl t at n r h mot x e and ph gocyt s w th tw lobed t ph l c t g nd d g t a l fill d w th ly d n l m t l N te th masse f e n l m t l fi ld All mag fi t e × 900 (C t y f ll g M M P .. Staff M t May Cl 24 34 237 Apr 27 1949)

obtained from venous blood of patients with acute dissem inated lupus erythematosus was then incubated with plasma bone marrow material obtained from patients with various other diseases Typical L E cells as well as the phenomena of nucleolysis and agglutination were observed

These observations on the L E cell add weight to the hypothesis that acute disseminated lupus erythematosus is a result of hypersensitivity The L E cell phenomenon is evidently immunologic in nature Use of peripheral blood in a procedure for diagnosis of lupus is possible but as yet would be premature Too few cases have been studied to establish its utility in this regard although it can be anticipated that a positive finding in examination of peripheral smears would have significance comparable to that of a similar finding in examination of bone marrow

[Leukocytes from the buffy coat of centrifuged samples of peripheral blood may also be incubated in the plasma to be tested —Ed.]

Lymphocytic Leukemoid Reaction of Blood Associated with *Miliary Tuberculosis* *Frank H Gardner and Stacy R* Mettier[5] (Univ of California) report two cases in which there was a lymphocytic leukemoid response to miliary tuberculosis Clinical diagnosis in both cases was lymphocytic leukemia but autopsies revealed diffuse miliary tuberculosis involving all hemopoietic tissues and no evidence of leukemic infiltration Both patients had granulocytopenia and anemia In one chronic tuberculosis was of 43 years and in the other of 28 years duration The findings emphasize that it may be impossible to distinguish between a terminal leukemoid blood picture and true leukemia There have been other reports of blood pictures similar to those of myelocytic and lymphocytic leukemia occurring in patients with miliary tuberculosis

Rossle observed patients with lymphocytic leukemia without adenopathy or hepatosplenomegaly but microscopic examination of bone marrow revealed leukemic infiltration In one of the authors cases autopsy findings of young and old tubercles throughout the organs and lymph nodes suggested repeated bacteremia Several sections of sternal and vertebral marrow revealed extensive single and conglomerate tubercle formation with striking caseation and trabecular bone destruction Aside from tubercle formation there were normal quantitative and qualitative relations of myelopoietic and erythropoietic series Megakaryocytes were adequate in number (Fig 79) The persistent lymphocytosis might result from persistent irritation of the lymphoid tissue and marrow by progressive miliary tuberculosis Feldman and Stasney ex

(5) Blood 4 767 775 J 1949

plained the myelocytic leukemoid blood response in tuberculous rabbits receiving tuberculin injections as an allergic response of bone marrow There is no experimental work to



Fig 9—Bon m ow Ep th l l p s u und d by m r w f mal arch te t e × 120 (C t y of Ga d e F H d M tt r S R. Blood 4 767 775 J n 1949)

indicate that lymphocytosis or a lymphatic leukemoid reaction is an allergic response to miliary tuberculosis

Rapid Slide Test for Heterophil Antibody in Infectious Mononucleosis William C Moloney and Lucy Malzone[6] (Tufts College) describe a practical screening test for detecting clinically significant amounts of heterophil antibodies in cases of infectious mononucleosis

METHOD—On a glass slide at room temperature 0 1 cc defibrinated sheep blood was mixed with 0 2 cc serum to be tested Results were positive only if 3 or 4 plus macroscopic clumping occurred within 30 60 seconds The heterophil antibody test was carried out on the same serums using the Paul Bunnell method and a serum dilution of 1 128 was considered the lowest positive level Sheep cells were preferably used fresh but defibrinated sheep blood kept at 5 C for two weeks gave reliable results Inactivation of serum was unnecessary Serums stored in the icebox lost potency slowly but if kept in the deep freeze the heterophil antibody was well preserved for long periods The heterophil antibody in infectious mononucleosis is active at 37 C as well as at lower temperatures

Of 41 patients with infectious mononucleosis the slide test

(6) Blood 4 72 7 J 1949

was positive for 35 and the Paul Bunnell test for 34 Of 53 patients with cirrhosis of the liver and 21 with acute infectious hepatitis the slide test was positive at room temperature for 7 with cirrhosis but negative for all at 37 C The Paul Bunnell reaction was negative for all Only 1 patient with multiple myeloma among 58 with a variety of neoplastic diseases had positive results in the slide test and none had positive Paul Bunnell reactions The serums of 95 pregnant women and 23 cord blood specimens showed no heterophil antibodies Results of Paul Bunnell and slide tests at 37 C were negative in seven patients with acquired hemolytic anemia Of 15 isoimmunized women only 1 had positive reactions to Paul Bunnell and slide tests The mother was O Rh positive and the father Rh positive A_1 A Their second child was A_2 O Rh positive An anti A agglutinin developed in the mother *The antibody in this case was apparently related to the Forssman type rather than that found in infectious mononucleosis*

The rapid slide test can give positive results with cold agglutinins (which may be abolished by warming to 37 C) or Forssman antibodies (which may be absorbed by guinea pig kidney) There was no evidence that blocking incomplete or hyperimmune heterophil antibodies occur in infectious mononucleosis

Rapid Macroscopic Test for Infectious Mononucleosis Method for Preservation of Sheep Cells The ordinary method of blood examination for heterophil antibodies is time consuming and requires fresh sheep blood F Rappaport (Tel Aviv) and M Skariton[7] (Petah Tikvah Israel) describe a rapid qualitative and quantitative method for determination of heterophil antibodies and a technic for preservation of sheep s blood cells

METHOD —The preliminary qualitative method is a slide agglutination te t In most ca es active serum is used To 1 drop of the unknown serum (fresh or inactivated) is added 1 loopful of concentrated sheep s blood corpuscles washed three or four times with saline solution the two are mixed thoroughly with a glass rod If no agglutination appears the serum is considered negative Typical agglutination constitutes a positive reaction and then requires quantitative evaluation

For quantitative evaluation a series of dilutions is made ranging from 1 7 to 1 3 584 Physiologic salt solution 0 4 ml is placed

(7) Am J Cl P th 19 665 667 J ly 1949

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Fig 79—Bone marrow Epithelioid ... by marrow of normal ... ture × 1 0 (Courtesy of Gardner F H and ... S R. Blood 4 767 75 June 1949)

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(6) Blood 4 722 27 J 1949

Gm per cent Patients with aplastic anemia required frequent transfusion whereas those with chronic agranulocytosis did not

Four patients were women and four patients were aged 22 27 when they came under treatment The woman aged 46 at the time leukopenia was recognized may well have had the disease many years Before agranulocytosis was diagnosed all had been exposed to factors which might possibly have dam aged bone marrow such as hair dye sulfonamides lead benzyl benzoate and mumps

The disease was characterized by attacks of severe infec tion from relatively trivial causes They included inflamma tion of the lips gums mouth and throat severe reactions to dental extraction otitis media digital and cutaneous sepsis suppurative lymphadenitis urinary infection septicemia and unexplained fever Intervals between attacks ranged from a few days to six years Between attacks the patients were fairly well though they lacked vitality Average duration of illness in the four survivors is now more than five years and there is no evidence of progressive deterioration

Marrow smears were cellular in two patients and acellular in three The main qualitative change was an increase in pro portion of myelocytes and a great decrease in proportion of segmented neutrophils The only remedy of proved efficacy was penicillin for control of acute attacks When bone marrow is cellular in patients of this type splenopathic neutropenia may be suspected but is unlikely in the absence of spleno megaly and increased blood destruction The authors suggest that these cases are variants of chronic aplastic anemia in which the main impact of the disease is on white cells

Cyclic Agranulocytosis Paul A Owren[9] (Univ Hosp Oslo) reports a case

Man 23 in spring 1939 had the first of many attacks of fever and sore throat which lasted a week and recurred in about 14 days Enlarged tonsils were found and since relapsing angina was sus pected as the cause tonsillectomy was done However relapses con tinued with surprising regularity for five years until death in 1944

Two days before each relapse the patient experienced fatigue anorexia and irritability Simultaneously or a little later sore pots appeared in the buccal mucosa Some became covered with grayish white masses surrounded by a red halo and others progressed to

(9) Acta med Scandina 134 87 97 1949

in the first tube and 0 25 ml in each of the remaining nine tubes To the first tube 0 1 ml patient s serum is added and mixed From this tube 0 25 ml is transferred to the second tube and mixed From the second tube 0 25 ml is transferred to the third etc To each tube 0 1 ml suspension of washed sheep cells is added Tubes are centrifuged immediately for two minutes at 3 000 rpm Results are read after gentle shaking The last tube containing single clumps indicates the limit of reaction

In the authors experiments every serum was tested by three methods the qualitative slide method the original Paul Bunnell method (with inactivated serum) and the quantitative rapid method Results obtained by these methods were identical The qualitative test first gives a positive result when the quantitative test shows agglutination in a dilution of 1 56 This limit should be regarded as suggesting infectious mononucleosis whereas a dilution of 1 112 constitutes a positive reaction

Since sheep s blood keeps in the refrigerator for only about five days it may be difficult in routine laboratory work to keep on hand a supply of sheep s blood that is satisfactory for use By addition of an equal part of 5 per cent Borax solution of pH 7 4 7 6 to defibrinated sheep s blood the latter can be preserved in the ice box for at least two months without undergoing hemolysis Addition of Borax does not interfere with the reaction

The authors method has the advantage that inactivation is omitted and results may be obtained quickly since it is not necessary to incubate for 2 hours or store on ice for 24 hours

Chronic Agranulocytosis E B Adams and L J Witts[8] (Radcliffe Infirm Oxford) studied five patients in whom neutropenia (neutrophil count below 1 500/cu mm) was apparently a primary condition The only constant features were leukopenia (total white cell count below 4 000/cu mm) and attacks of agranulocytic infection There was no evidence of increased blood breakdown no deficiency of iron or liver and no leukemic or other infiltration Mild anemia was present in some of the five and the distinction between chronic agranulocytosis and aplastic anemia is an arbitrary one It was the authors practice to diagnose aplastic anemia in patients of this type if the hemoglobin without treatment was below 10 Gm per cent and chronic agranulocytosis if it was above 10

(8) Quart J Med 18 173 185 July 1949

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(9) A ta m d Sca d a 134 87 97 1949

mucosal necrosis leading to deep ulcerations accompanied by regional swelling of lymph nodes and rise in temperature Ulcerations were localized to the inner side of lips and cheeks tonsillar region and posterior pharyngeal wall Temperature rose evenly to 102.2 104 F and returned by lysis to normal in a few days Regularly during febrile periods heavy gingivitis developed with edematous and bleeding interdental papillae purulent secretion and intense halitosis Some relapses were associated with necrotic ulcerations of skin in the anal region face and extremities The primary eruptions were vesicles which ruptured and gave rise to ulcerations Several attacks were associated with conjunctivitis When attacks were over ulcerations healed rapidly

The highest granulocyte counts were found in the first half of the symptom free interval During the following days the granulocyte count rapidly decreased until there was complete agranulocytosis or severe granulocytopenia one to three days before the next temperature rise The agranulocytic phase lasted three to five days and then while the temperature fell granulocytes again increased The postfebrile increase of granulocytes was associated with a shift to the left with numerous staff cells metamyelocytes and some myelocytes *in the peripheral blood At the same time pronounced toxic granulation appeared Eosinophils and basophils showed* no definite cyclic changes but monocytes showed slight cyclic changes in the opposite direction to the granulocytes Lymphocyte count remained normal Plasma cells appeared in small numbers toward the end of the agranulocytic phase Hemoglobin level and red cell counts remained normal Marrow granulocytopoiesis showed cyclic variations in constant relation to peripheral blood findings Clinical examination of the patient otherwise revealed normal findings

All remedies suggested in the literature for cyclic agranulocytosis were used but none was effective These included pentnucleotide roentgen treatment liver therapy long term vaccination with hemolytic streptococci vitamins blood transfusions antiallergic treatment with epinephrine ephedrine salicylic acid and detoxin and finally splenectomy The only effective measure used was antibiotic treatment of the mouth infection a result rather than a cause of agranulocytosis

Because of the theory that cyclic agranulocytosis results from an allergic reaction with neutralization of antibody *followed by re*action free antianaphylactic period cutaneous tests were made with a series of antigens Results however were equivocal Minimal doses of hemolytic streptococci produced extremely strong reactions with large infiltrations and formation of secondary abscesses but repeated injection did not show any clearcut effect on granulocyte counts or cyclic variations in bone marrow

The theory has been proposed that granulocytopenia results from excessive leukolysis in the spleen and a case of relapsing agranulocytosis has been reported in which symptoms disappeared after splenectomy Negative result of

splenectomy in the present case however suggests that the spleen is not important in the pathogenesis of cyclic agranulocytosis

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LEUKEMIAS AND RELATED DISORDERS

The first two articles demonstrate that diagnosis from bone marrow biopsy is possible only when typical cellularity can be demonstrated. For this reason conditions with late or nonhomogeneous involvement of the bone marrow are unlikely to be susceptible of early diagnosis by bone marrow puncture It is a good general rule that without definite disturbance of the peripheral blood picture (indicating diffuse marrow involvement) marrow biopsy will not be diagnostic In the lymphoma group the difficulty of diagnosis even from sections of lymph nodes means that needle biopsy of the marrow will be as futile as is usually needle biopsy of a definitely involved lymph node In our hands needle biopsy of the bone marrow is used largely as a procedure confirmatory of a diagnosis usually inferred from peripheral blood examination If a cellular marrow is not clearly in evidence it then becomes necessary to carry out trephine biopsy to determine the nature of the hyperplasia whether fatty fibrotic or otherwise —Ed.

Evaluation of Sternal Aspiration as Aid in Diagnosis of Malignant Lymphomas In Hodgkin s disease thoracic and abdominal nodes are involved much more commonly than are the superficial cervical nodes Because of the inaccessibility of thoracic and abdominal nodes for biopsy Talbert Cooper and Charles H Watkins (Mayo Clinic) attempted to evaluate clinical usefulness of sternal bone marrow aspiration for obtaining material of diagnostic significance in malignant lymphoma

Simple needle *aspiration of sternal bone marrow* was performed on 15 unselected patients with Hodgkin s disease 10 with lymphosarcoma and 2 with follicular lymphoma Diagnosis was based on results of lymph node biopsy autopsy or both With the Illinois sternal aspiration needle about 2 cc sternal marrow substance was aspirated and transferred immediately to a paraffin lined container and mixed gently with a minute pinch of heparin powder as an anticoagulant Grossly visible particles of marrow substance were smeared gently on the surface of a glass slide

Criteria used for diagnosis of Hodgkin s disease of bone marrow were similar to those used for its diagnosis in other tissues and organs Hyperplasia of reticular cells is often the

(2) Blood 4 534-549 May 1949

dominant change However because Hodgkin s is characterized by pleomorphism diagnosis rests finally on demonstration of Reed Sternberg cells There is no certain way of distinguishing these cells from megakaryocytes However nuclei of Reed Sternberg cells are round oval lobulated multilobed or multinucleated whereas megakaryocytic nuclei though often multilobed are always single with generous more uniformly distributed chromatin and a fine chromatin parachromatin pattern The outstanding characteristic of the Reed Sternberg cell is the prominent nucleolus which is usually lacking in the megakaryocyte or megakaryoblast Cytoplasm of the normal megakaryocyte contains characteristic azurophilic granulation when stained with polychrome dyes In addition pseudopodia with apparent platelet formation are often observed The generous cytoplasm of the Reed Sternberg cell has a faintly basophilic granular appearance with Wright s stain and the cell membrane is often indistinct Satisfactory section preparations were obtained in nine instances but in none were lesions suggestive of Hodgkin s disease demonstrable Lesions of bone marrow in Hodgkin s disease may be focal and of microscopic proportions or extensive and grossly demonstrable When small focal lesions exist chance alone might account for disappointing results on attempted needle aspiration

In lymphosarcoma all elements of the normal lymph node may be represented and there is no diagnostic cell Cells range from typical small lymphocytes through larger atypical cells with indented hyperchromatic nuclei and relatively little cytoplasm to lymphoblastic cells with reticular nuclear structure sometimes containing nucleoli and a basophilic often vacuolated cytoplasm Lymphocytic lymphoblastic and reticulum cell varieties of lymphosarcoma have been commonly described In 7 of the 10 cases of proved lymphosarcoma abnormal lymphocytic cell types were encountered on sternal aspiration and in 3 cases bone marrow infiltrations diagnostic of lymphosarcoma were demonstrated in fixed section preparations

In two cases of follicular lymphoma specimens of sternal marrow presented no striking abnormalities However because of the apparently close relation of this disease to lymphosarcoma it is felt that study of a larger number of cases

may prove the procedure to be of some diagnostic value The authors conclude that as an aid to diagnosis in obscure malig nant lymphoma sternal aspiration is likely to prove of great est value in lymphosarcoma [in which surgical biopsy of a lymph node is usually possible and certainly far more satis factory —Ed]

Sternal Marrow Studies in Hodgkin s Disease Review of Literature and Report of 35 Cases On the basis of their study Louis R Limarzi and Jerome T Paul[3] (Univ of Illi nois) conclude that the most constant finding in bone marrow in Hodgkin s disease is myeloid and megakaryocytic hyper plasia The morphologic pattern of the granulopoietic tissue is that seen in chronic toxic states The panhyperplasia of bone marrow simulates that of Banti s disease (splenic ane mia) A pathologic type of megakaryocytopoiesis involving the lymphoid megakaryocytes is observed in some cases of Hodgkin s disease These produce atypical forms of platelets Reed Sternberg cells are not seen in aspirated sternal marrow or in histologic sections of bone marrow particles from such material Detailed cytologic studies on bone marrow mega karyocytes in cases of Hodgkin s disease indicates that the giant cells in Hodgkin s granuloma are not similar or related to the platelet forming cell The finding of increased num bers of normal or atypical plasma cells eosinophils and reticular cells is neither a constant nor a specific pattern of the bone marrow in Hodgkin s disease Eosinophilia of bone marrow cannot be correlated with peripheral blood eosino philia

Evidence at hand definitely indicates that the cellular mar row elements removed by sternal aspiration in most cases of Hodgkin s disease are not obtained from the pleomorphic lesion characteristic of Hodgkin s granuloma There are sev eral reasons for this failure to observe the specific tissue in sternal aspirated material not every sternum is involved in Hodgkin s disease the scattered specific focal lesions usually occupy such a small proportion of the marrow cavity that on the basis of chance they may not be aspirated by the sternal needle the specific lesions in bone marrow tend to have much fibrous tissue making aspiration more difficult The authors emphasize that unless specific tissue is observed

(3) Am J Cl n P th 19 929 961 O t be 1949

dominant change However because Hodgkin s is characterized by pleomorphism diagnosis rests finally on demonstration of Reed Sternberg cells There is no certain way of distinguishing these cells from megakaryocytes However nuclei of Reed Sternberg cells are round oval lobulated multilobed or multinucleated whereas megakaryocytic nuclei though often multilobed are always single with generous more uniformly distributed chromatin and a fine chromatin parachromatin pattern The outstanding characteristic of the Reed Sternberg cell is the prominent nucleolus which is usually lacking in the megakaryocyte or megakaryoblast Cytoplasm of the normal megakaryocyte contains characteristic azurophilic granulation when stained with polychrome dyes In addition pseudopodia with apparent platelet formation are often observed The generous cytoplasm of the Reed Sternberg cell has a faintly basophilic granular appearance with Wright s stain and the cell membrane is often indistinct Satisfactory section preparations were obtained in nine instances but in none were lesions suggestive of Hodgkin s disease demonstrable Lesions of bone marrow in Hodgkin s disease may be focal and of microscopic proportions or extensive and grossly demonstrable When small focal lesions exist chance alone might account for disappointing results on attempted needle aspiration

In lymphosarcoma all elements of the normal lymph node may be represented and there is no diagnostic cell Cells range from typical small lymphocytes through larger atypical cells with indented hyperchromatic nuclei and relatively little cytoplasm to lymphoblastic cells with reticular nuclear structure sometimes containing nucleoli and a basophilic often vacuolated cytoplasm Lymphocytic lymphoblastic and reticulum cell varieties of lymphosarcoma have been commonly described In 7 of the 10 cases of proved lymphosarcoma abnormal lymphocytic cell types were encountered on sternal aspiration and in 3 cases bone marrow infiltrations diagnostic of lymphosarcoma were demonstrated in fixed section preparations

In two cases of follicular lymphoma specimens of sternal marrow presented no striking abnormalities However because of the apparently close relation of this disease to lymphosarcoma it is felt that study of a larger number of cases

may prove the procedure to be of some diagnostic value The authors conclude that as an aid to diagnosis in obscure malig nant lymphoma sternal aspiration is likely to prove of great est value in lymphosarcoma [in which surgical biopsy of a lymph node is usually possible and certainly far more satis factory —Ed]

Sternal Marrow Studies in Hodgkin's Disease Review of Literature and Report of 35 Cases *On* the basis of their study Louis R Limarzi and Jerome T Paul[3] (Univ of Illi nois) *conclude that the most constant finding in bone marrow* in Hodgkin s disease is myeloid and megakaryocytic hyper *plasia The morphologic pattern of the granulopoietic tissue* is that seen in chronic toxic states The panhyperplasia of bone *marrow simulates that of Banti s disease* (splenic ane mia) A pathologic type of megakaryocytopoiesis involving the lymphoid megakaryocytes is observed in some cases of Hodgkin s disease These produce atypical forms of platelets Reed Sternberg cells are not seen in aspirated sternal marrow or in histologic sections of bone marrow particles from such material Detailed cytologic studies on bone marrow mega karyocytes in cases of Hodgkin s disease indicates that the giant cells in Hodgkin s granuloma are not similar or related to the platelet forming cell The finding of increased num bers of normal or atypical plasma cells eosinophils and reticular cells is neither a constant nor a specific pattern of the bone marrow in Hodgkin s disease Eosinophilia of bone marrow cannot be correlated with peripheral blood eosino philia

Evidence at hand definitely indicates that the *cellular* mar row elements removed by sternal aspiration in most cases of *Hodgkin s disease are not obtained from the pleomorphic* lesion characteristic of Hodgkin s granuloma There are sev eral reasons for this failure to observe the specific tissue in sternal aspirated material not every sternum is involved in Hodgkin s disease the scattered specific focal lesions usually occupy such a small proportion of the marrow cavity that on the basis of chance they may not be aspirated by the sternal needle the specific lesions in bone marrow tend to have much fibrous tissue making aspiration more difficult The authors emphasize that unless specific tissue is observed

(3) Am J Cl P th 19 929 961 O tob 1949

Hodgkin s disease should not be diagnosed Individual marrow cells or groups of cells as seen in sternal aspirated material are not sufficient evidence on which to diagnose Hodgkin s disease The marrow smear itself does not reveal any pattern diagnostic of the disease Accurate diagnosis of the disease is established only by the finding of the specific pleomorphic lesion of Hodgkin s granuloma This is best observed in histologic section of an involved lymph node

↓ Owing to the infrequency of amyloidosis as a result of chronic sepsis, its association with other diseases as in the following article becomes of increased interest —Ed

Amyloidosis in Hodgkin's Disease is discussed by Stanley L Wallace Daniel J Feldman Irving Berlin Charles Harris and Irving A Glass[4] (New York City) Although association of amyloidosis and Hodgkin s disease has been known for a long time review of the literature reveals only 29 cases of Hodgkin s disease in which concurrence of amyloidosis was demonstrated histologically or suggested by clinical studies

From analysis of these cases and of one observed by the authors coexistence of Hodgkin s disease and amyloidosis appears to be more than a coincidence All reported cases are typical of the secondary type of amyloidosis i e involvement chiefly of the liver spleen kidneys and adrenals In primary amyloidosis the heart lungs skin mucous membranes and tongue are usually involved Although a small percentage of primary cases may show a secondary type of distribution the fact that all available reported cases fall into the latter category tends to rule out a casual association of Hodgkin s disease and primary amyloidosis There seems to be no association between amyloidosis and any specific form of Hodgkin s disease since reported cases fall into all categories and have the same sex and age distribution as Hodgkin s disease in general

Hepatosplenomegaly cannot be used with certainty in determining presence or absence of amyloid disease Although amyloidosis is frequently characterized by hepatosplenomegaly so is uncomplicated Hodgkin s disease Nor can presence of edema ascites or hydrothorax be used in differential diagnosis since these conditions can be produced by compression of various blood vessels and lymphatic chan

(4) Am J M d 8 552 557 Ap I 1950

nels by Hodgkin s tissue as well as by hypoproteinemia secondary to the albuminuria of renal amyloidosis However uncomplicated Hodgkin s disease even with renal involvement has not been reported as producing albuminuria In 11 of 15 adequately studied cases of associated amyloidosis and Hodgkin s disease pronounced albuminuria was noted In three of the other four cases at least a trace of albumin was found in the urine It can therefore be presumed that proteinuria occurring during Hodgkin s disease points to a complicating factor and amyloidosis must be carefully searched for as a possible cause of the urinary findings Congo red tests were made in five reported cases and in the authors case All could be interpreted as positive if 60 100 per cent absorption of congo red from the blood is considered diagnostic of amyloid disease It is therefore concluded that presence of proteinuria and significant absorption of congo red from the blood are the most reliable criteria for determining presence of amyloid in Hodgkin s disease

Chronic Nonleukemic Myelosis Report of Six Cases is made by Clarence Merskey[5] (Univ of Capetown South Africa) The name chronic nonleukemic myelosis seems appropriate for certain conditions described under a wide variety of other names (chronic splenomegaly with anemia and myeloid reaction of blood splenomegaly of myeloid type without myelocythemia myeloid megakaryocytic splenomegaly splenomegaly with myeloid transformation hepatolienal hemopoietic endotheliosis and agnogenic myeloid metaplasia) All these refer to a condition in which there may or may not be anemia but in which there are usually primitive red and white cells in peripheral blood though the great increase in leukocytes characteristic of leukemia is usually absent The spleen is enlarged and at autopsy foci of extramedullary hemopoiesis may be found in spleen and liver and to a lesser extent in other organs such as kidneys and lymph nodes The essential feature is hyperplasia of leukopoietic tissues which results in an increase in white count and in a degree of immaturity in white cells of peripheral blood Bone marrow especially shows gross overgrowth of cells of the myeloid series though even in marrow the hyperplasia appears relatively orderly in nature Consequently marrow does not display the invasive char

(5) A h. I t M d. 84 277 292 A gu t 1949

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the worse the prognosis and the greater the disability The more the condition resembles nonleukemic myelosis the more chronic the disease and the better the prognosis The disease was chronic in these six patients In five anemia was either absent or mild in none were myeloblasts found in peripheral blood even myelocytes were scanty in four patients total white cell count showed all grades of increase but in general was less than that characteristic of chronic myeloid leukemia Immature red cells were found only in small numbers in peripheral blood

This syndrome is also related to polycythemia vera and forms a connecting link between polycythemia vera and true leukemia Merskey suggests that the syndromes of polycythemia vera nonleukemic myelosis and true leukemia and even possibly osteosclerosis and myelofibrosis have a common genesis

↓ The following four articles are concerned with multiple myeloma a neoplastic disease usually considered to be due to plasma cell proliferation The increasing use of plasma protein determinations and especially of needle puncture of the bone marrow is leading to more frequent diagnosis of the condition — Ed

Multiple Myeloma Willis M Fowler and Jack D Gordon[6] (State Univ of Iowa) analyzed clinical and laboratory findings in 52 patients with multiple myeloma This disease was first recognized by presence of a substance in the urine now known as Bence Jones protein For a long time Bence Jones proteinuria was considered one of the important diagnostic criteria but it is now known that it occurs in only about half the patients with multiple myeloma and also in patients with other types of bone lesions In addition Bence Jones proteinuria may appear only intermittently rather than constantly In the present series it was encountered in 34 6 per cent of patients in whom urine tests were done Its presence or absence in an individual case has limited diagnostic value and no prognostic significance nor can its presence be correlated with the presence of ordinary albuminuria or with plasma protein level When found in urine however Bence Jones protein suggests multiple myeloma and should lead to further diagnostic procedures

Multiple myeloma occurs in the later decades and is more common in men than in women Pain usually in the back

(6) Am P t. 1 449 460 M y 1950

acteristics seen in true leukemia The course is prolonged anemia tends to be slight and disability is often negligible for some years Bone marrow is not leukemic in that it does not show immaturity at the myeloblast level which is characteristic of true leukemia nor are myelocytes necessarily numerous Nevertheless the condition may be only a mild variant of leukemia differing only in degree rather than in any fundamental characteristic.

In the six cases studied by Merskey the clinical picture was not particularly characteristic All patients were elderly and in all the disease followed a somewhat symptomless course. Chief symptoms were general such as vague feelings of ill health and lack of strength and were usually related to degree of anemia In two cases the red cell count was normal One patient had mild and another severe anemia whereas in two patients the count almost reached polycythemic levels Thrombocyte number was within normal range in four patients but in two it was 1 500 000 and more/cu mm White cells were increased in all patients and showed varying degrees of immaturity two patients showed immature red cells as well None had myeloblasts in peripheral blood but in all the cells of the polymorphonuclear leukocyte series were grossly increased both relatively and numerically There were no constant correlations between increases in red cell series in white cell series and in thrombocytes Autopsy material demonstrating hyperplasia of bone marrow was available in two cases and in three others hyperplasia in situ was shown in sections of bone marrow taken during life

This rather mixed collection of cases included one case of true chronic myeloid leukemia one of osteosclerosis with myeloid reaction one of possible chronic hemolytic anemia and three of (possibly) nonleukemic myelosis It was not possible to make a diagnosis during life in the case of osteosclerosis despite x ray examination of bones and biopsy of aspirated marrow sections Chronic hemolytic anemia can usually be diagnosed but in this patient the only evidence of that disease was a consistently elevated reticulocyte count the patient refused marrow aspiration The real difficulty in diagnosis lay in differentiation of these disorders from true chronic myeloid leukemia Differences were really only in degree It appears that the greater the incidence of leukemic features

localized to a single or a few foci the process is usually gen eralized and typical myeloma or plasma cells are evident in the sternum ribs ilium or vertebra in the early stages This procedure has also emphasized how frequently the lesion is of the plasma cell type The number of plasma cells seen on a marrow smear is variable but in the authors expe rience is greater than 10 per cent of nucleated cells The ma ture plasma cell is usually oval with a deep blue cytoplasm having an irregular or blotchy staining reaction It appears to contain bluish granules although granules as such are

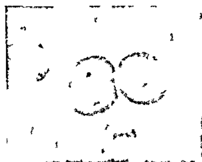


Fig 80—G p f f pl m ll w th tw mmat f m (Cou te y f F wl W M d G don J D Am P t 1 449 460 M y 1950)

seldom found There may be a perinuclear clear or light stain ing area or the light staining area may be ovoid and located at the side of the nucleu rather than encircling it In the im mature cell the outline is often irregular Vacuolation of the cytoplasm is frequent and the nucleus is usually eccentrically placed and small dark and round (Fig 80) Some idea as to prognosis and rapidity of progress of the disease in an indi vidual case may be gained from the frequency of mature forms in the sternal marrow The more chronic and slowly progressive cases tend to have a predominance of mature cells

Multiple Myeloma as Form of Leukemia Michael A Rubinstein (New York City) presents evidence that the gen erally accepted points of distinction between multiple mye loma and leukemia cannot be regarded as fundamental and that there is no sharp demarcation between the two diseases

There are often features of leukemia in multiple myeloma

(7) Blood 4 1049 1066 S pt mb 1949

was the most frequent complaint of patients in this series Pathologic fractures accounted for pain in some instances but in many others there was no obvious explanation and x rays failed to reveal any lesion in the skeletal structure in the region of the pain Weakness developed during the illness in all patients and was a major complaint of 23 on admission In 20 patients neurologic complications were present in 6 as the outstanding feature The multiple small circumscribed osteolytic lesions found in the bones on roentgen examination are the most typical and outstanding manifestation of the disease Diffuse osteoporosis is also a common but less striking manifestation but it is often overlooked

The cause of the bleeding tendency in multiple myeloma has not been adequately explained In none of the nine cases in which it was present was hemorrhage severe enough to affect the course The importance of hyperproteinemia and hyperglobulinemia in this disease has been repeatedly emphasized Rapid sedimentation rate autohemagglutination and unusual rouleaux formation which may be encountered in peripheral blood of multiple myeloma patients seem to be a function of or to be dependent on hyperproteinemia Though the electrophoretic pattern of plasma or serum is abnormal in most if not all cases of multiple myeloma electrophoretic studies cannot be considered an important diagnostic aid until the chemical structure of the proteins producing the abnormal patterns is clarified Elevated serum calcium is found in 30 50 per cent of cases but serum phosphorus is normal or low except when there is renal insufficiency Alkaline phosphatase is normal Renal complications are found in 50 70 per cent of cases

Hemoglobin below 12 Gm./100 cc and a red cell count below 4 000 000 was found in 43 cases in this series Anemia was slightly hypochromic as a rule The total leukocyte count was within normal limits in 40 cases and was above 10 000 in only 4 Differential count was normal in all but two cases In only one were plasma cells found in the peripheral blood stream One might expect to encounter plasma cells in peripheral blood far more frequently than is the case since such cells are found within vessels in the region of the tumor

Bone marrow aspiration in multiple myeloma has emphasized that although roentgen evidence of the disease may be

Cryoglobulin Present in High Concentration in Plasma of Case of Multiple Myeloma Cryoglobulins are the class of proteins in which precipitate on cooling of plasma and redissolve *on warming* Robert M Hill Stuart G Dunlop and Richard M Mulligan[8] (Univ of Colorado) report the case of a patient with multiple myeloma whose blood solidified quickly in the needle and syringe while it was being drawn even though large amounts of anticoagulant were used However when the syringe and needle were warmed this did not occur When 7 5 ml heparinized blood was kept at 37 40 C and centrifuged there was a 3 ml upper layer of apparently normal plasma a 2 8 ml middle clear *almost water white layer* and a 1 7 ml lower layer of cells On cooling the upper layer remained liquid but the middle layer congealed to a pearly white translucent solid On warming the middle layer became liquid After a whole blood transfusion separation into three layers never occurred though the whole blood or plasma solidified on cooling as before The urine was free from protein at all times

Viscosity of the patient s plasma was more *than five times* that of normal plasma at 38 C and rapidly increased to infinity at 32 C Separated cryoglobulin gave strong biuret xanthoproteic Millon and Acree Rosenheim reactions and a negative Molisch reaction Cholesterol ester crystals were obtained and probably represented a lightly bound lipid fraction of the protein molecule Micro Kjeldahl analysis showed an average of 15 13 per cent nitrogen content By microbiologic assay 10 amino acids were detected The amino acid pattern suggested a relation to beta or gamma globulins All of the analyses physical properties and behavior toward sodium sulfate fractionation of the cryoglobulin were compatible with its classification as a pseudoglobulin

Terminally total protein was 18 1 Gm per cent of which 9 8 Gm per cent was globulin This amount of globulin reflects the tremendous terminal metabolic activity of the neoplasm itself

Treatment of Multiple Myeloma with Urethane William J Harrington and William C Moloney[9] (Tufts College) treated 11 patients with multiple myeloma with urethane

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(8) J Lab & Cl Med 34 1057 1065 Aug t, 1949
(9) L nc 3 253 71 M b 1950

In addition to the well known circumscribed tumor formation diffuse infiltration of the bone marrow also exists in multiple myeloma Cases of diffuse infiltration without evidence of circumscribed tumor formation are known Lack of circumscribed tumor formation does not rule out the possibility of multiple myeloma Extraskeletal visceral myelomatous spread involving the kidney spleen lymph nodes etc occurs in some cases of multiple myeloma Not only visceral organs but blood itself may be invaded by myeloma cells Although massive invasion of peripheral blood so as to produce the picture of plasma cell leukemia occurs rarely occasional myeloma cells may be found in concentrated smears (corresponding to the aleukemic forms of leukemia) even though they may be missed on routine examination Increased uric acid content of the blood and elevated basal metabolism characteristic of leukemia are frequently seen also in myeloma Though the accepted textbook view is that myeloma is a disease of older age isolated instances of myeloma in younger age groups including infancy have been observed Whereas in most cases symptomatology of multiple myeloma is due to tumor involvement of bones in a number of patients complaints are not referable to the osseous system and may be similar to those ordinarily found in leukemia

On the other hand there are often features of myeloma in leukemia Rare cases of leukemia have been reported in which only bone marrow was involved These rare forms would correspond to the usual forms of multiple myeloma limited to bone marrow and without visceral involvement Less uncommon is involvement of different bones in leukemia Lesions may take the form of tumors destruction and absorption of bone leading to fractures or periosteal elevations and arthritis Bence Jones proteinuria and hyperproteinemia admittedly typical of multiple myeloma have also been occasionally observed in leukemia Sometimes symptoms referable to bones and joints dominate the clinical picture of leukemia

Rubinstein concludes that the difference between myeloma and leukemia as far as the conventional distinguishing features are concerned is merely one of incidence what is rare in one disease is common in the other and vice versa Multiple myeloma is probably a leukemia of plasma cells ordinarily of aleukemic type

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(8) J L b & Cl M d 34 1057 1065 A g t 1949
(9) C 3 253 71 M h 1950

Dosage was usually 3 6 Gm daily given orally Six patients apparently responded clinically and from the laboratory stand point Five patients died one of intercurrent disease Another patient was in an advanced stage of the disease and died within two weeks after start of urethane therapy Three pa tients received adequate doses of urethane but failed to re spond Because of immature characteristics of myeloma cells in the bone marrow and rapid clinical course these patients were considered to have an acute form of multiple myeloma Experience with urethane in myelogenous leukemia indicates that these acute forms will probably not respond to urethane whereas the drug may bring about effective remissions in the more chronic forms

Clinical improvement was striking All nine patients with bone pain were greatly relieved In the six patients with a good clinical response weight gain was a conspicuous finding and three patients showed striking improvement in hemo globin and red cell levels There were also reduction in ab normal serum proteins and suppression of myeloma cell pro liferation in the bone marrow No statistical validity can be attached to figures regarding length of survival in 11 cases However mean survival time for all 11 cases is 21 months and average survival time 25½ months These figures are already better than those recently reported in 55 cases followed from onset of symptoms to death

It has been pointed out that urethane may cause gastro intestinal disturbances and serious leukopenia Use of spe cially coated tablets in this study appreciably lessened the tendency to nausea and vomiting and frequent blood studies furnished warning of impending leukopenia Withdrawal of urethane and prophylactic use of antibiotics have prevented to date any serious sequelae to suppression of white blood cells

Urethane is not a cure for multiple myeloma and expe rience with many more cases will be necessary before its thera peutic usefulness can be adequately evaluated Nevertheless in a disease which has been so persistently resistant to all forms of therapy results of urethane administration to this group of patients suggest that multiple myeloma may be added to the growing list of neoplastic diseases that may be come subject to chemotherapeutic control

Treatment of Acute Leukemias of Childhood with Folic Acid Antagonists Eugene J Weber Felix E Karpinski Jr and Robert W Heinle[1] (Western Reserve Univ) treated 24 children with acute leukemia by administration of the folic acid antagonists aminopterin and A methopterin Hematologic or symptomatic improvement or both occurred in 20 When diagnosis was established intramuscular injection of 1 mg aminopterin daily was begun The drug was discontinued when toxic lesions occurred or hematologic depression was noted After an observation interval treatment was resumed 1 mg being given intramuscularly every second day If this wa well tolerated and peripheral counts remained stabilized the pa tient was discharged to be observed in the clinic three times weekly Aminopterin was given on each clinic visit according to an arbitrary schedule generally depending on the leukocyte count (over 6 000/cu mm 1 mg 2 000 6 000/cu mm 0 5 mg and under 2 000/cu mm none)

Roentgen changes of the skeleton were seen in 13 children on initial examination Skeletal lesions developed in three others during treatment Four types were observed osteoly sis radiolucent transverse bands osteosclerosis and subperios teal new bone formation

All patients followed a similar hematologic course Initial response was depression of bone marrow with reduction of all elements normal and abnormal Nucleated cell count of the marrow regularly fell to 400 000 500 000/cu mm (normal for the method used 1 000 000 2 000 000/cu mm) Peripheral blood showed anemia and leukopenia This phase was concur rent with initial intensive therapy Megakaryocytes and plate lets were decidedly reduced and bleeding tendencies occurred With discontinuance of the antagonist cellularity of marrow increased and normal cells returned in greater numbers The most normal marrow was found four to six weeks after ther apy was instituted In several patients abnormal marrow cells dropped to less than 1 per cent of the total and peripheral blood studies were entirely within normal limits Despite con tinued therapy however the number of abnormal cells in marrow gradually increased Appearance of abnormal cells in peripheral blood was delayed often not occurring until more than 75 per cent of marrow cells were abnormal In a

(1) J P diat 36 69 78 J a ry 1950

few patients a second and fatal hematologic depression occurred after long continued therapy Terminal course of these patients was that of an aplastic anemia At autopsy it was possible to demonstrate severe hypoplasia of the marrow and frequently there was little or no evidence of leukemia

Toxic lesions observed in these patients were limited to mucosal ulcerations of the mouth (Fig 81) accompanied by some degree of fever Lesions were erythematous patches with an ulcerated necrotic center which ultimately healed with for



F g 81—T c lce at n of t ng and l p s o d y s an pt n th py (Cou tesy of W be E J et al J Ped t 36 69 8 J nua y 1950)

mation of a heavy crust Attempts to hasten healing by administration of crude liver extracts and folic acid were not successful The most effective treatment consisted of administration of sulfadiazine by mouth and topical application of an aqueous solution of gentian violet

Mechanism of action of folic acid antagonists is thought to be production of a folic acid deficiency However when three children who had attained hematologic and symptomatic remissions were placed on daily oral doses of *20 30 mg* folic acid marrow peripheral blood and clinical course were unaltered after three to four weeks indicating that the occurrence of relapse was not accelerated by administration of folic acid in this dosage

Although folic acid antagonists did not constitute a satisfactory form of therapy for leukemia they were more effective than other forms of treatment

↓ The final articles in this ection d al with the use of the so called nitrogen mustards There is now a new compound melamine which can be given orally and is aid to be free from the side effects on the ga tro inte tinal tract of the older drugs As it is still in the stage of clinical trial its comparative efficiency remains to be established. Our own view about these drugs is that they are chiefly u eful only when x ray cannot for one reason or another be employed Th se circumstances are defined in the following abstracts—Ed.

Treatment of Malignant Disease with Nitrogen Mustard N B Kurnick Karl R Paley Mack H Fieber and D K Adler (Mount Sinai Hosp New York City) report results in 64 patients with malignant diseases treated with HN_2 Of these 24 had Hodgkin s disease 4 chronic lymphatic leuke mia 2 chronic myelogenous leukemia 10 lung carcinoma 2 Wilms tumor 1 breast carcinoma 1 anaplastic metastatic carcinoma 1 melanocarcinoma 8 lymphosarcoma 2 mycosis fungoides 1 chronic nonleukemic myelosis 3 reticulum cell sarcoma 1 spindle cell sarcoma 1 miliary tuberculosis 1 Boeck s sarcoid and 2 malignancy of undetermined nature All but eight were given HN_2 in the usually recommended dose of 0 1 mg /kg on each of four successive days the eight received 10 mg daily for four days Twenty patients received two to six such courses

Results in general agreed with those of other investigators Favorable results comparable with those obtained with radio therapy followed HN treatment in most cases of Hodgkin s disease Fever when present subsided dramatically by the third day Sense of well being and regression of lymphade nopathy were usually noted during the first post treatment week whereas hepatosplenomegaly receded during the second week Contrary to earlier reports striking reduction in spleen size was common In a few cases pain due to bone lesions re sponded satisfactorily One patient who had become resis tant to roentgen rays responded to HN and was subsequently sensitive to radiotherapy Relapses occurred in all cases in a few days to 10 months In most cases remissions became pro gressively shorter with successive courses of HN Chronic lymphatic leukemia lymphosarcoma mycosis fungoides and reticulum cell sarcoma showed variable responses Carcinomas were uniformly unresponsive except for one bronchogenic adenocarcinoma and one Wilms tumor One patient with chronic nonleukemic myelosis was dramatically benefited

(2) A I t M d 30 974 1003 M y 1949

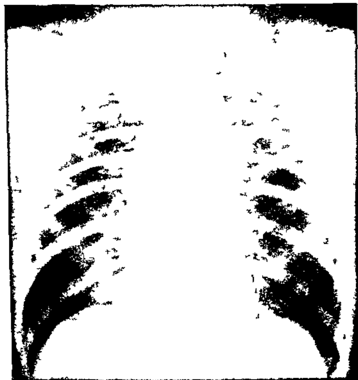
with diminution in spleen size and restoration of normal blood picture No cures were observed However in one proved case of generalized Hodgkin s disease only one small splenic granuloma with degenerative changes could be found at autopsy Death was due to agranulocytosis and thrombocytopenia secondary to excessive therapy The almost complete suppression of granulomatous disease suggests the desirability of using maximal tolerated dosage The authors recommend that the therapy schedule be revised to provide for an initial series of closely spaced courses for maximal therapeutic effect perhaps to be followed by regularly spaced maintenance doses

Toxic reactions were the same as those previously reported and were thought to be unrelated to injection rate Nausea and vomiting occurred in almost all cases but was often milder with successive injections No appreciable relief was obtained with pyridoxine atropine teropterin® or sedation Numerous visceral function tests revealed no changes attributable to HN_2 therapy except the hemopoietic response Lymphopenia u u ally occurred between the third day of treatment and the second post treatment day Leukocyte counts below 3 000 occurred in almost every case with the minimal count 3 25 days after treatment (average 11 days) infection was rare even with counts below 1 000 Anemia secondary to treatment was noted only twice and thrombocytopenia was noted seven times with bleeding four times Hemotoxic effect was entirely unpredictable nor was its severity related to response of the primary disease Teropterin® had no effect in preventing the myelotoxic effect or in hastening recovery

HN_2 therapy is of value in Hodgkin s disease occasionally in lymphosarcoma and mycosis fungoides and probably in nonleukemic myelosis but it is of no value in carcinoma In cases of widespread or inaccessible lymphomatous lesions in which roentgen therapy is not feasible HN is particularly useful Fever due to lymphomas responds much more regularly to chemotherapy than to irradiation In moribund patients the more rapid and occasionally dramatic effect of HN is advantageous Constrictive lesions of the great vessels or the spinal cord often respond more rapidly to the chemical agent than to roentgen rays Initial swelling of tumor tissue often seen after x ray therapy was not observed with HN

Radiotherapy remains the preferred treatment for readily accessible or localized lesions

Treatment of Lymphomas and Other Neoplastic Diseases with Nitrogen Mustard Louis K. Alpert Ezra M Greenspan



F g 8 —Hodgk di E l g d m d t l lymph od bef e HN the py (C t y f Alp rt L K. *t al* An I t. M d 3 393 432 M h 1950)

and Stanley S Peterson[3] review results in 52 patients with various lymphomas and other neoplastic diseases treated with HN_2 at Walter Reed Hospital Favorable though temporary effects were observed in most of 27 patients with Hodgkin's disease 3 with giant follicular lymphoblastoma and 2 with lympholeukosarcoma (Sternberg) In patients with lympho

(3) A I t M d. 32 393 43 M h 1950

with diminution in spleen size and restoration of normal blood picture No cures were observed However in one proved case of generalized Hodgkin s disease only one small splenic granuloma with degenerative changes could be found at autopsy Death was due to agranulocytosis and thrombocytopenia secondary to excessive therapy The almost complete suppression of granulomatous disease suggests the desirability of using maximal tolerated dosage The authors recommend that the therapy schedule be revised to provide for an initial series of closely spaced courses for maximal therapeutic effect perhaps to be followed by regularly spaced maintenance doses

Toxic reactions were the same as those previously reported and were thought to be unrelated to injection rate Nausea and vomiting occurred in almost all cases but was often milder with successive injections No appreciable relief was obtained with pyridoxine atropine teropterin* or sedation Numerous visceral function tests revealed no changes attributable to HN_2 therapy except the hemopoietic response Lymphopenia usually occurred between the third day of treatment and the second post treatment day Leukocyte counts below 3 000 occurred in almost every case with the minimal count 3 25 days after treatment (average 11 days) infection was rare even with counts below 1 000 Anemia secondary to treatment was noted only twice and thrombocytopenia was noted seven times with bleeding four times Hemotoxic effect was entirely unpredictable nor was its severity related to response of the primary disease Teropterin* had no effect in preventing the myelotoxic effect or in hastening recovery

HN_2 therapy is of value in Hodgkin s disease occasionally in lymphosarcoma and mycosis fungoides and probably in nonleukemic myelosis but it is of no value in carcinoma In cases of widespread or inaccessible lymphomatous lesions in which roentgen therapy is not feasible HN_2 is particularly useful Fever due to lymphomas responds much more regularly to chemotherapy than to irradiation In moribund patients the more rapid and occasionally dramatic effect of HN_2 is advantageous Constrictive lesions of the great vessels or the spinal cord often respond more rapidly to the chemical agent than to roentgen rays Initial swelling of tumor tissue often seen after x ray therapy was not observed with HN

Although the most important toxic effects were observed in the hemopoietic system panhematopenia only occasionally limited treatment Development of moderate leukopenia was considered an indication of effective dosage Since leukopenia was usually of short duration white cell counts as low as 2 000/cu mm were not considered a contraindication to HN_2 therapy Thrombocytopenia and purpura was the most serious complication encountered

Nitrogen mustard therapy appeared to be most suitable in the following clinical types of Hodgkin s disease (1) wide spread involvement which cannot be treated adequately with x ray (2) lymphadenopathy with *striking constitutional* symptoms (fever weight loss etc) (3) fever without demon strable enlarged nodes (occult febrile type) (4) visceral involvement and (5) terminal cases which have become re sistant to roentgen therapy Radiation was the therapy of choice in patients with relatively localized disease in periph *eral mediastinal or retroperitoneal regions obstructive* lesions around the spinal cord biliary tract ureters or great vessels bone involvement and fibrosing Hodgkin s disease Figure 82 shows enlarged mediastinal lymph nodes with Hodgkin s disease before HN therapy There was complete shrinkage of hilar lymphadenopathy after one course Despite three additional courses (total dose 134 mg) mediastinal adenopathy recurred as illustrated in Figure 83

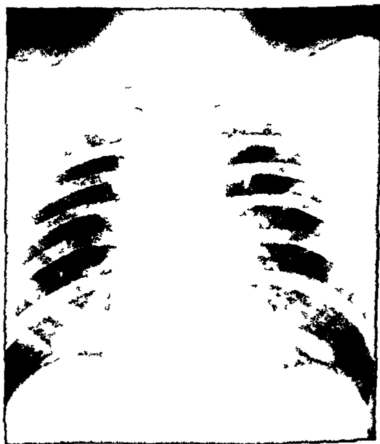
PURPURAS

The first two art cles in this section are general surveys of the hemor rhag c states and of thrombopenic pu pura re pectively They should be tudied in the orig nals for much that cannot be included in abstracts —Ed

Etiology and Management of Hemorrhagic Diatheses are discussed by Charles A Doan[4] (Ohio State Univ) When few or no blood platelets are found in blood of any patient with purpura study of bone marrow is essential to determine whether this deficit is secondary to bone marrow megakary ocytic inadequacy or excessive splenic demand (*Fig 84*) Generalized purpura is frequently the first sign of progres

(4) A I t M d 31 967 988 Decemb 1949

sarcoma reticular cell sarcoma chronic lymphatic leukemia subacute myeloid leukemia sarcoidosis and various carcinomas little or no significant benefit resulted even though varying degrees of tumor shrinkage were produced In only



Fg 83—Rec e of m d t n l ad p thy n the m p t t 18 mo th ft HN th apy wa beg n F u of t e tm t (tot l do e 134 mg) w gi en d g th s nter l (Co t y f Alp t L K t l A I t M d 32 393 432 Ma ch 1950)

two patients was Hodgkin s disease adequately controlled for more than a year with repeated courses of HN alone In 17 patients x ray therapy was necessary to produce longer remissions than were obtained with HN_2

disappearance of all purpuric manifestations Toxic marrow destruction or inhibition may result from chemicals physical agents roentgen rays and radioactivity and infections Careful supravital study of fresh living marrow in thrombocytopenic purpura at once reveals clearly and unequivocally any specific damage to megakaryocytes which may be responsible for the circulating platelet deficit Vacuolated nuclei and cytoplasm with chromatin karyorrhexis and increased phagocytosis of specific cellular debris are unmistakable evidences of such toxic damage Elimination of the offending agent accompanied by supportive fresh blood transfusions permits regeneration of megakaryocytes Splenectomy in selected instances is followed by marrow recompensation

When peripheral thrombocytopenia has been found associated with clinical purpura and bone marrow studies not only fail to reveal cellular aplasia displacement damage or toxicity but actually reflect an excessive multiplication of megakaryocytes the more mature units showing active cytoplasmic platelet fragmentation in the living supravital preparations the conclusion is justified that despite the apparently uninhibited compensatory megakaryocytic hyperplasia the peripheral platelet demand is in excess of the available supply When the spleen is not demonstrably enlarged primary splenic thrombocytopenic purpura is the most likely diagnosis

The adrenalin test may reveal hypersequestration of platelets by a normal sized spleen indicative of a primary specific withdrawal or inhibition of circulating platelets in primary hypersplenic thrombocytopenic purpura (Werlhof s disease) When there is an obvious splenic enlargement with adrenalin test evidence of specific platelet hypersequestration and bone marrow shows only compensatory megakaryocytosis without myelophthisic or toxic marrow damage a hypersplenic syndrome secondary to some other disseminated constitutional disease must be considered Primary splenic Hodgkin s granuloma splenic Gaucher s disease chronic leukemic involvement of the splenic parenchyma by any cell type tuberculosis or tertiary syphilis of the spleen congestive splenomegaly secondary to myocardial decompensation acute splenic tumor of infectious etiology all have been associated with hypersplenic thrombocytopenic purpura Emergency splenectomy should be performed on exactly the same reasoning as for primary

sive marrow hypoplasia When on repeated studies of bone marrow obtained from the manubrium and the body of the sternum from selected spinous processes and from the crest of the ilium no megakaryocytes are found but there is definite evidence of a beginning marrow pancytopenia and when neither past personal history nor direct investigation reveals toxic environmental medicinal or bacterial factors primary hypoplasia with or without osteofibrosis or osteopetrosis mechanisms may be established In a certain proportion of such patients extramedullary hemopoiesis in spleen and liver

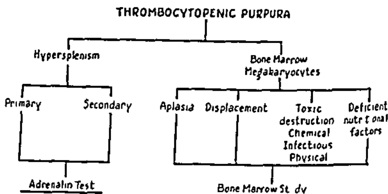


Fig 84 (Courtesy of Doan C A Ann. Int. Med. 31 967 988 December 1949)

may partially compensate for marrow hyperplasia In early stages with only moderate marrow hypoplasia splenectomy may be followed by a remission of months or years Replacement of fresh citrated blood transfusions is the treatment of choice for primary marrow aplasia Polycythemic donors have made particularly effective blood contributors Generous use of any or all of the presently known stimulatory and maturing factors for blood cells liver folic acid vitamin B_1 etc have thus far failed to affect marrow regeneration in this type of patient

In certain naturally occurring circumstances in persons with food idiosyncrasies or gastrointestinal abnormalities concerned with disturbed digestion and absorption thrombocytopenic purpura on a deficiency basis secondary to general marrow hypoplasia may occur Correction of any specific deficiency is followed by regeneration of megakaryocytes and

disappearance of all purpuric manifestations Toxic marrow destruction or inhibition may result from chemicals physical agents roentgen rays and radioactivity and infections Careful supravital study of fresh living marrow in thrombocytopenic purpura at once reveals clearly and unequivocally any specific damage to megakaryocytes which may be responsible for the circulating platelet deficit Vacuolated nuclei and cytoplasm with chromatin karyorrhexis and increased phagocytosis of specific cellular debris are unmistakable evidences of such toxic damage Elimination of the offending agent accompanied by supportive fresh blood transfusions permits regeneration of megakaryocytes Splenectomy in selected instances is followed by marrow recompensation

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hypersplenism regardless of the known presence of serious disease elsewhere in the body

When normal or excessive numbers of platelets are found in circulating blood of patients with purpura immediate studies are indicated to differentiate between specific plasma and/or capillary defects It is now routine to determine prothrombin plasma level in every patient showing any hemorrhagic tendency Low prothrombin levels cause purpura in hemorrhagic disease of the newborn in obstructive jaundice in liver disease in persons on a low vitamin K diet and in patients with hyperperistalsis or other intestinal conditions preventing proper vitamin K absorption

Bleeding after extensive irradiation or nitrogen mustard administration has been attributed to excess of heparin or heparin like substances Protamine or toluidine blue dye are effective in controlling hemorrhage from these causes Recurring if not constantly demonstrable abnormally prolonged coagulation time without thrombocytopenia warrants diagnosis of hemophilia Fresh whole blood fresh plasma or freshly frozen or lyophilized plasma from normal donors which contain antihemophilic globulin reduce the prolonged in vitro coagulation time as does plasma fraction I of Cohn available through the American Red Cross Afibrinogenemia occurs rarely as a congenital and usually familial disease and may be treated with fresh blood or plasma transfusions

Hereditary telangiectasis is of more cosmetic than hemorrhagic significance In hereditary pseudohemophilia there is inherent inability of the capillary wall to contract following injury leading to a prolonged bleeding time in a patient with nonthrombocytopenic purpura Fresh whole blood transfusions produce the best therapeutic results

Possibility of anaphylactoid purpura may be elucidated by careful history and skin and dietary elimination tests Antihistaminic drugs are sometimes helpful or desensitization with histamine diphosphate or an autogenous urinary proteose concentrate may produce remission

Problem of Essential Thrombocytopenic Purpura is discussed by Charles F Stroebel Donald C Campbell and Albert B Hagedorn[5] The cause of this condition is not known Ac

(5) M Cl North Am 33 1027 1046 J ly 1949

cording to one view there is excessive destruction of platelets by the spleen Another view suggests that the spleen elaborates *some substance which suppresses formation of platelets* from the megakaryocytes The fact that splenectomy is of some benefit in this disease indicates that the spleen somehow plays a role in its mechanism The objection to the concept of hypersplenism is that splenectomy does not benefit all patients One might conclude that some cellular system such as the histiocytic plays a major role and that splenectomy is of value because it removes a large depot of histiocytes Microscopic study of the spleen reveals no consistent abnormal pattern Grossly the spleen is little if at all enlarged A third view points to capillary abnormality and suggests that thrombocytopenia occurs because of an excessive demand for platelets to close capillary defects The recent suggestion that blood of some patients with this disease and with certain other diseases associated with abnormal bleeding contains an excess of heparin like substance is still being investigated The role of allergic response also needs further study

Diagnosis depends on recognition of abnormal capillary fragility and thrombocytopenia and exclusion of known *causes of these conditions Purpura is manifested by bright* red to purple macules which later turn brown and fade because of disintegration of hemoglobin and absorption of hemosiderin Purpura is gross external evidence of a break *in continuity of small blood vessels One of the simplest meth*ods of producing purpura is with the tourniquet test in which capillaries of the forearm are distended by elevation of venous pressure to a level just above diastolic pressure The sphygmomanometer cuff is applied in the usual place Bleeding time is obtained by observing the time required for a small inflicted wound to stop bleeding If capillaries are normal the time usually does not exceed five minutes Periods beyond 10 minutes indicate abnormal capillaries Purpura is seen in many conditions not associated with thrombocytopenia Addition of thrombocytopenic to the diagnostic term depends on laboratory demonstration of reduction of platelets in circulating blood In essential thrombocytopenic purpura blood coagulation time is normal but the clot does not retract normally Clot retraction is thought to be a function of platelets

There are three general types of nonthrombocytopenic

purpura (1) Allergic purpura is seen in association with other manifest allergic disorders (2) Symptomatic purpura occurs in acute infectious diseases after snake bites and sometimes after ingestion of certain drugs e g belladonna copaiba iodides quinine mercurials bismuth and salicylates Purpuric manifestations are sometimes seen in advanced renal and cardiac disease Scurvy may also be classified as symptomatic purpura (3) Idiopathic purpura includes nonthrombocytopenic purpuric bleeding from the gastrointestinal tract (Henoch s purpura) and the rheumatic purpura of Schonlein

Certain other nonthrombocytopenic hemorrhagic conditions must also be distinguished In some persons bleeding from wounds may be excessive bleeding time prolonged and tourniquet test positive Purpura is not a prominent feature and platelet count coagulation time and clot retraction are normal This type of disease is called pseudohemophilia Exclusion of other forms of nonthrombocytopenic bleeding disease involves recognition of the bleeding time in *hemophilia* fibrinopenia and hypoprothrombinemia

When purpura and thrombocytopenia occur other conditions and agents which produce these manifestations must be excluded such as ingestion of certain chemicals (sedormid® gold salts sulfonamides phenobarbital benzene nitrogen mustards dinitrophenol quinine ergot bismuth arsenicals and iodides) radiation therapy myelogenous and lymphocytic leukemia lymphoblastomas aplastic anemia and myelophthisic anemias caused by metastatic carcinoma and chronic intoxications Sternal aspiration is of value in excluding these diseases Thrombocytopenia is not infrequently seen in certain chronic diseases involving splenomegaly such as Gaucher s disease Felty s syndrome Banti s disease and Hodgkin s disease and in definite parenchymal hepatic disease

Review of the records of 99 women and 51 men with essential thrombocytopenic purpura showed that about 18 per cent of women noted menorrhagia at onset of menstruation as their first symptoms Onset was before age 40 in over two thirds of the patients Increased incidence of other diseases producing secondary thrombocytopenic purpura developing after age 40 should make search for the primary disease all the more rigorous in this age group A family history of bleeding disease was rare though there were three instances

of transient thrombocytopenic purpura in babies born of mothers with the disease

Of 59 adults treated by splenectomy 84 7 per cent had satisfactory immediate response 10 2 per cent were unimproved and 5 1 per cent died in the immediate postoperative period Of 26 adults not treated by splenectomy 42 3 per cent had an immediate spontaneous remission lasting at least six months 26 9 per cent continued to have purpura and 30 8 per cent died within three months of cerebral hemorrhage Of 20 children 90 per cent had a good immediate result after splenectomy whereas 10 per cent continued to have mild purpura Of 11 children who did not have splenectomy 73 per cent recovered spontaneously and 27 per cent continued to have purpura There were no deaths in either group Splenectomy is recommended but long time prognosis should be guarded because of possible recurrences Previous duration or character of the disease postoperative behavior size or histologic appearance of the spleen and postoperative platelet response give no sure clue as to the future course of the disease

Three Cases of Thrombocytopenic Purpura Occurring after Rubella with Review of Purpura Associated with Infections J F Ackroyd[6] observed three cases of thrombopenic purpura following rubella during an epidemic in the spring of 1940 All showed purpura and ecchymosis 3 11 days after onset Two patients recovered spontaneously but 1 died of cerebral hemorrhage nine days after onset When first observed there were too few platelets in the blood of all three patients to permit counting In the two survivors platelets had returned to normal 20 days later and initial capillary fragility had decreased One patient re examined six months later was entirely normal

Although only seven well authenticated and six doubtful cases of thrombopenic purpura after rubella have been reported the occurrence in less than six weeks of three cases is a high incidence This epidemic was characterized by an abnormally large proportion of cases in which other complications developed suggesting that it might have been due to an unusually virulent virus possibly one with an exceptional tendency to cause purpura Therefore in addition five cases of uncomplicated rubella in the same epidemic were studied

(6) Quart. J M d 18 99 318 Octbe 1949

In these platelet count was usually low and capillary fragility high at onset of the disease returning to normal during convalescence changes in erythrocytes leukocytes bleeding and coagulation time were observed Degrees of thrombopenia and increased capillary fragility after infections of apparently equal severity varied strikingly from one patient to another Since these changes are known to occur in other acute infectious diseases and the incidence of purpura never appears to bear any relationship to severity of the disease it is concluded that degrees of thrombopenia and increased capillary fragility depend on susceptibility of the tissues of a patient rather than on intensity of the primary infection

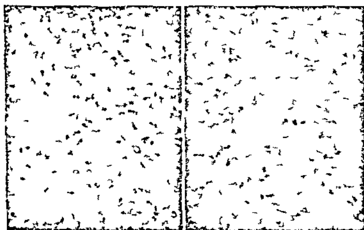
There are two striking facts in connection with this type of purpura (1) Purpura may occur in severe cases or may complicate very mild infections (2) Purpura may occur either during the acute stages of infection or during convalescence Different degrees of increased capillary fragility and thrombocytopenia appearing early in the disease and persisting for varying periods have been demonstrated in the cases reported here It seems probable that purpura occurring early represents a high grade of susceptibility In other patients the existence of a symptom free period before onset of purpura suggests the possibility of an allergic basis similar to that to which nephritis after streptococcal infections has been attributed

↓ The following article is important because it critically analyzes the mechanism of a type of purpura due to drug sensitivity —Ed

Mechanism of Reduction of Clot Retraction by Sedormid* in Blood of Patients Who Have Recovered from Sedormid* Purpura When sedormid* is added to blood of patients who have recovered from sedormid* purpura clot retraction is reduced and in some patients platelets are agglutinated These effects are not seen in blood of normal persons It is well known that if platelets are removed from plasma by centrifugation or by action of an antiplatelet serum clot retraction is reduced or even abolished It therefore seemed that action of sedormid* in reducing clot retraction might be due to an effect on platelets Since agglutination of platelets could not be demonstrated in blood of all patients in whom sedormid* caused reduced clot retraction however it seemed possible that this reduction was due to an effect of sedormid* on some

other part of the clotting mechanism J F Ackroyd (St Mary s Hosp Med School) added fibrinogen thrombin and platelets to different samples of the blood of patients who had recovered from sedormid® purpura and investigated action of sedormid® on clot retraction on the supposition that a normal clotting factor might replace one sensitive to sedormid® and so permit normal clot retraction in presence of the drug

Addition of fibrinogen to the blood of such patients or to normal blood reduced clot retraction When sedormid® and



F g 85 (l ft) —Ph tom g ph f pl tel t h pla m f m p ti t wh h d co d f om sedo m d® pu pu t k n 0 m te fte l w dd d Cl co ta me pl t l t

F g 86 (ght) —Ph t m g ph f sam p t ent pl m tak 0 m t fte d l t n w h t t d l t on f sed m d® l Platel t l t b p ac lly ll de g ly

(C t y f Ack yd J F Cl S 8 23 7 D mbe 1949)

fibrinogen were added to the blood of sedormid® sensitive patients reduction in clot retraction was greater than with either alone When thrombin was added to normal blood or to that of patients who had recovered from sedormid® purpura clot retraction was generally slightly reduced When thrombin and sedormid® were added simultaneously to the blood of such patients the thrombin lessened the reduction in clot retraction due to the sedormid ® but if sedormid® was allowed to act for

(7) Cl n. Sc. 8 235 67 Dec mbe 1949

five minutes before thrombin was added its action in reducing clot retraction was unimpaired There was thus no evidence that either fibrinogen or thrombin was concerned in action of sedormid® on clot retraction Thrombin seemed merely to accelerate coagulation and to prevent sedormid® from acting as completely as usual

In blood of patients who had recovered from sedormid® purpura observed microscopically during coagulation in the presence of sedormid® platelets were lyzed with abnormal rapidity (Figs 85 and 86) This presumably explains the action of sedormid® in reducing clot retraction because if platelets are removed from blood clot retraction is invariably abolished Excessive amounts of sodium citrate prevented the action of sedormid® on clot retraction apparently by protecting platelets from abnormal lysis by sedormid® during coagulation

Addition of normal platelets to normal blood or to the blood of sedormid® sensitive patients did not affect clot retraction Addition of normal platelets to the blood of a sedormid® sensitive patient to produce a final concentration of about 140 000/cu mm of added platelets did not improve clot retraction in presence of sedormid® though this concentration of platelets is sufficient to restore normal clot retraction to the plasma after its clot retraction had been abolished by centrifuging out the platelets If normal platelets were added to the platelet free plasma of patients recovered from sedormid® purpura and the plasma was subsequently clotted in the presence of sedormid® platelets were lyzed abnormally rapidly and clot retraction was greatly reduced If platelets of sedormid® sensitive patients were added to normal platelet free plasma which was then clotted in the presence of sedormid® platelets were not lyzed abnormally rapidly and clot retraction was normal If excessive amounts of platelets were added to a sensitized person s plasma which was then clotted in presence of sedormid® not all the platelets were abnormally lyzed because the drug and those remaining were able to promote normal clot retraction If a sufficiently large excess of platelets was added to whole blood action of sedormid® on clot retraction was entirely abolished

The author concludes that sedormid® reduces clot retraction in the blood of patients recovered from sedormid® pur

pura by causing lysis of platelets during coagulation this is the only factor involved Platelet lysis results from action of some factor in the plasma and is not due to any peculiarity of the platelets themselves

↓ The next three articles indicate the trend of important recent evid nce *to the effect that platelet deficiency causes a coagulation defect* This is rarely demonstrable by the crude technic of the coagulation test but none theless is clearly hown by the d tective prothrombin consumpt on m e method devi ed by Quick —Ed

Coagulation Defect in Thrombocytopenic Purpura Normal coagulation time observed in thrombocytopenic purpura has always puzzled students of coagulation and has led many to conclude that coagulation is not disturbed in this disease Recently evidence however shows that coagulation time may not always be a reliable measure of true coagulability It has long been recognized that in hypothrombinemia the coagulation time determination i much too insensitive to serve as a guide for estimating severity of prothrombin deficiency As a result of development of the prothrombin time determination rapid progress both clinical and theoretical ensued in the group of diseases in which prothrombin deficiency occurs With development of the prothrombin consumption time (serum prothrombin time) determination which measures quantitatively the factors responsible for activation of prothrombin a new approach is offered for study of hemorrhagic diseases due to coagulation defects which are not in the prothrombin complex i e diseases in which prothrombin time is normal

Absence of clot retraction which is characteristic of severe thrombocytopenic purpura should no doubt be considered a coagulation defect Although it is recognized that clot retraction depends on intact platelets a quantitative correlation between number of platelets and speed and degree of clot retraction was difficult to make until introduction of silicone (Dri film) which made it possible to secure and keep native plasma with a minimum of platelet lysis

Armand J Quick Jacob N Shanberge and Mario Stefanini[8] (Marquette Univ) correlated prothrombin consumption (obtained with the aid of silicone coated glassware) with the quantitative estimation of clot retraction and the platelet

(8) J Lab & Cl n M d 34 761 767 J e, 1949

count of whole blood and of normal human native plasma from 20 normal adults and applied these findings to clinical thrombocytopenic purpura

In thrombocytopenic purpura delayed clot retraction and poor prothrombin consumption closely paralleled the low platelet count Prothrombin consumption time and speed of clot retraction simultaneously and promptly returned to normal as platelet count increased and clinical condition improved Platelet count prothrombin consumption and clot retraction responded quickly to splenectomy in one case of idiopathic thrombocytopenic purpura

The prothrombin consumption test supplies the first strong evidence that a coagulation defect is present in thrombocytopenic purpura The test offers a new measure of platelet activity which is postulated to be that of activating plasma thromboplastinogen Clot retraction likewise is a measure of intact platelet activity When the test is carried out on native plasma it has quantitative significance since the beginning and completion can be accurately determined by direct visual observation and no correction is required for cell volume

Factor in Serum Which Accelerates Conversion of Prothrombin to Thrombin Its Relation to Coagulation Defect of Thrombocytopenic Blood The exact role of the platelet in blood coagulation is the subject of considerable controversy Although thrombocytopenic plasma exhibits retarded coagulation a prolonged clotting time is rare in thrombocytopenic purpura This has been explained by the theory that even in severe thrombocytopenia sufficient thromboplastin is elaborated to produce normal coagulation The hemorrhagic manifestations of thrombocytopenic purpura have generally been ascribed to a great reduction in blood platelets to capillary dysfunction or to inadequate clot retraction rather than to abnormalities in coagulation itself

Benjamin Alexander and Andre de Vries[9] (Boston) present observations which indicate that coagulation of thrombocytopenic blood is profoundly disturbed In a previous article an agent in serum was described which accelerates conversion of prothrombin to thrombin in presence of thromboplastin plus calcium The agent serum prothrombin conversion accelerator (SPCA) is measured by the enhancement in per

(9) Blood 4 747 751 June 1949

cent of the prothrombin activity of normal oxalated plasma induced by the admixture to it of serum obtained from the blood in question one hour after coagulation Before the test the serum is oxalated then incubated for one half hour to inactivate thrombin

Ten subjects with thrombocytopenic purpura were studied All had platelet counts below 100 000/cu mm Mean SPCA activity was 33 per cent in contrast to 99 per cent for 95 normal subjects *Residual serum prothrombin activity* averaged 50 per cent compared with 6 per cent for normal persons No strict correlation was evident between bleeding time or platelet count and SPCA or residual serum prothrombin activity although subjects with the highest platelet counts seemed to have the highest SPCA activities Coagulation times of most of the patients were within normal range That the clotting times were essentially normal in these patients despite the clotting defect reflects the lack of sensitivity of this test Addition of normal platelets or thromboplastin corrected the observed abnormalities in SPCA and residual prothrombin activity In one subject the clotting defect persisted despite temporary remission of the thrombocytopenia consequent to splenectomy

Observations on Coagulation Defect in Thrombocytopenic Purpura While utilizing small amounts of heparin for prolonging coagulation of blood by the method of Waugh and Ruddick T Lyle Carr and Willis M Fowler[1] (State Univ of Iowa) noted that some patients who were actively bleeding had an augmented reaction to heparin

Technic—Nine Wassermann tubes are used Tube 1 remains empty until blood is added and tube 2 contains 0 5 cc of 0 9 per cent normal saline Serial dilutions of heparin in 0 5 cc saline are added to the remaining seven tubes so that tube 3 receives 0 1 unit heparin tube 4 receives 0 2 unit heparin and so on until tube 9 receives 0 7 unit heparin To each tube is added 1 cc blood and the time which elapses from the moment blood is first seen in the withdrawal syringe until coagulation occurs is the end point in that particular tube

When the Waugh Ruddick test was performed on 30 normal subjects coagulation time in tubes 1 and 2 which contained no heparin varied from 4 to 12 minutes A gradual increase in time required for coagulation was found as greater amounts of heparin were encountered Coagulation ultimately

(1) J Lab & Cl M d 34 12 7 1 37 S ptembe 1949

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(9) Blood 4 747 751 Jun 1949

This reaction is not like that produced by intravenous injection of commercial heparin Increased susceptibility of thrombocytopenic blood to heparin apparently is not due to an increased amount of circulating heparin like substance

Adhesiveness of Blood Platelets in Thromboembolism and Hemorrhagic Disorders Measurement of Platelet Adhesives by Glass Wool Filter Because of the possibility that blood coagulability is related not only to the number of circulating platelets but also to their adhesiveness many methods have been devised to study platelet adhesiveness Sylvan E Moolten and Leo Vroman[2] (New Brunswick N J) devised a *method in which a wick of braided glass wool is used as an* absorbing filter for separation of adhesive from nonadhesive platelets in citrated blood thus making possible enumeration of their relative proportions in the total platelet count

Technic —Commercial glass wool is drawn into three strands of equal size and worked into a loose braid 0 5 1 cm thick A segment 6 7 cm long is cut and split a short distance at one end to provide three supporting arms by which the braid is suspended vertically in a silicone coated test tube of 2 cm internal diameter The arms are secured over the rim of the tube by an elastic band The filter is readied for use by moistening it with 1 5 ml physiologic saline covering the upper end with a loose fitting Bakelite cap to prevent evaporation and warming it to 37 C Blood 1 8 ml is *quickly drawn from the subject s vein into a silicone-coated syringe containing 0 2 ml of 3 8 per cent sodium citrate solution mixed and* transferred to a silicone coated collecting tube A prefiltration platelet count is made immediately Ten minutes after the blood is drawn 1 ml is permitted to drip into the glass wool as quickly as possible without overflow or leakage Thirty seconds later the blood in the braid is washed through with 8 ml of chilled eluting fluid consisting of 1 part of 3 8 per cent sodium citrate solution added to 9 parts of physiologic saline cooled before use to about 5 C The washed braid is removed the filtrate mixed well and a postfiltration platelet count done The sample is drawn into a white cell counting pipet to the 0 5 mark and diluted *to the 11 mark with formalinized citrate solution.* (The prefiltration platelet count is made by drawing the sample into a red cell counting pipet to the 0 5 mark and diluting to *the 101 mark with the same solution) After the sample is shaken* standard hemocytometer chambers are filled with the respective cell suspensions and permitted to settle Counts are made of the red blood cells in 5 small squares and of the platelets in 25 small squares When their number appears significantly less than normal platelets are enumerated in five large squares and the total divided by 5 Data for each sample (filtered and unfiltered) are charted as fol

(2) Am J Clin P th 19 701 09 A gu t 1949

occurred in 40 90 minutes In no instance was blood rendered incoagulable under these conditions

When the Waugh Ruddick test was performed on 15 patients with bleeding tendencies associated with primary or secondary thrombocytopenia coagulation time was essentially normal in the first two tubes which did not contain heparin but was decidedly prolonged in the remaining tubes containing serial dilutions of heparin Fluctuations were noted in speed of coagulation in individual patients from time to time when there was no significant change in number of platelets but when there were active clinical hemorrhagic tendencies the increased sensitivity to heparin was always present Variations in Waugh Ruddick test results more nearly paralleled clinical manifestations of hemorrhage than did the platelet level In these patients coagulation required 45 100 minutes in the presence of 0 1 unit heparin and in many instances blood was incoagulable in the fourth tube and in all subsequent dilutions These results show that coagulation time in such patients is normal in the absence of heparin but is decidedly increased with even small amounts of heparin and the blood is easily rendered incoagulable

In four of seven patients with thrombocytopenia administration of protamine sulfate and toluidine (1 4 mg/kg body weight) apparently shortened coagulation time in tubes containing 0 1 and 0 2 unit heparin and occasionally in the tube containing 0 3 unit heparin but had no effect on tubes containing a higher concentration This suggests that protamine in the blood stream was sufficient to neutralize 0 1 0 3 unit heparin but not larger amounts In two patients protamine sulfate and toluidine had no demonstrable effect and in the remaining patient the material was given concomitantly with a spontaneous remission

Waugh Ruddick test was done on five patients before and after splenectomy In four operation brought about complete remission by clinical and laboratory standards In all these patients Waugh Ruddick test results also returned to normal In the fifth patient operation was followed by an immediate but moderate rise in platelet count and a normal Waugh Ruddick curve Two months later cutaneous hemorrhages had reappeared platelet count had dropped and the Waugh Ruddick curve was again prolonged

bleeding time normal clotting time increased capillary fragility and poor clot retraction The diagnosis of thrombasthenia or pseudohemophilia was justified since in this syndrome platelet count is usually normal bleeding time is variable clotting time of venous blood may be normal or increased clot retraction is usually normal but may be poor and capillary fragility may be normal or strikingly increased Absence of a bleeding tendency in the family does not exclude this interpretation Other data also were like those found in thrombopenic purpura namely high residual serum prothrombic activity and prolonged recalcification time Since addition of normal platelets to plasma from the patient rectified the clotting defect and conversely addition of platelets from the patient to normal plasma deprived of its platelets did not correct the induced abnormality it must be concluded that the patient s platelets were inherently defective and unable to function normally Addition of normal platelets to thrombopenic blood similarly corrects the clotting defect Thus except for the normal number of platelets blood from the patient was indistinguishable from thrombopenic blood

Platelet count in this patient later dropped to thrombopenic levels suggesting a possible relation between thrombasthenia and idiopathic thrombopenic purpura It is suggested that idiopathic thrombopenic purpura is sometimes preceded if only for a short time by abnormal platelets that are removed from the circulation The following method for measuring functional capacity of platelets is suggested

TECHNIC —The platelets are added to normal plasma deprived of its platelets with precautions against platelet breakdown The mixture is recalcified and residual serum prothrombic activity determined Normally no prothrombin should be demonstrable The amount of prothrombin remaining in the serum is a measure of thromboplastin evolving from the platelets since all other clotting factors important in prothrombin conversion will have been provided or adequately controlled

Disseminated Arteriolar and Capillary Platelet Thrombosis Morphologic Study of Its Histogenesis Ira Gore[4] (Armed Forces Inst of Pathology Washington D C) reviews five cases of disseminated arteriolar and capillary platelet thrombosis Significant clinical features are insidious onset of vague nonlocalizing symptoms fever purpura anemia and

(4) Am J P th 26 155 1 5 J y 1950

lows (1) red blood cells/5 small squares (2) platelets/25 small squares × 2 (3) total red blood cells corrected for added citrate (4) total platelets corrected for added citrate (5) red blood cell platelet ratio (6) adhesive index—value for red blood cell platelet ratio of filtered sample — that of the unfiltered sample Using the empirically found adhesive index of 0 7 as representing zero adhesiveness numerical approximation of the number of adhesive platelets may be made by the following calculation nonadhesive platelets = total platelets — adhesive index + 0 3 adhesive platelets = total platelets — nonadhesive platelets

The normal range of adhesive platelet count was found to be between 60 000 and 110 000 platelets/cu mm and the adhesive platelet count in individual normal persons was found to vary less from time to time than the total platelet count The glass wool filter method of measuring platelet adhesiveness is relatively simple and can be readily applied clinically as an aid to detection of predisposition to thrombosis and related conditions

[It is possible that as also suggested by Wiener purpura occurring with relatively normal platelet counts may be due to defective platelet function This is also suggested by the following report of defective prothrombin consumption in the blood of such a patient —Ed]

Thrombasthenia and Thrombocytopenic Purpura Report of Case Demonstrating Qualitative and Quantitative Inadequacy of Platelets is made by Benjamin Alexander and Greta Landwehr[3] (Harvard Univ) Although the role of platelets in the hemostatic mechanism is not entirely understood it is clearly established that reduction in platelet number is associated with hemorrhagic phenomena prolonged bleeding time abnormal clot retraction and disturbed capillary retractility The degree of thrombopenia necessary to induce clinical and laboratory manifestations of purpura varies from patient to patient suggesting that qualitative differences in the platelets are important Furthermore existence of normal platelet counts in cases which have many features commonly associated with thrombopenic purpura indicates that the quality of platelets in these patients may be poor In the case observed such aberrations in platelet function actually occurred

The patient a man aged 40 had normal platelet counts early in the disease Nevertheless the following salient clinical manifestations of thrombopenic purpura were present bleeding into the skin and from mucous membranes increased

(3) New E gl d J Med 241 965 968 D c. 15 1949

sues This seemed to be the reverse of what would be anticipated if the lesions were secondary to spontaneous agglutination in the circulating blood On the other hand when a section included an appreciable length of an involved vessel propagated platelet thrombi covered by a sleeve of hyperplastic endothelium were often observed The proliferating plump investing endothelial cells contrasted sharply with the flat tenuous lining of the occluded vessel and indicated an origin from a portion of the vessel not always in the plane of the tissue section Careful search revealed focal lesions of arterioles and capillaries on which platelet thrombi formed and from whence they grew along the length of the vessel

These focal lesions termed prethrombotic were rare The lesion consisted of a segmental accumulation of hyaline material beneath the endothelium of a capillary and between the endothelium and musculature of an arteriole (Fig 87) In focal areas swelling of this homogeneous substance bulged both into the vessel lumen carrying with it the overlying endothelium and externally producing a defect in the vessel wall Although the nature of this change cannot be established by ordinary histologic technic this swelling of the hyalin can best be explained by imbibition of fluid from circulating blood At any rate the swelling evidently progressed until there was a break in the overlying endothelium whereupon platelets accumulated rapidly to cover the defect Presumably the small caliber of vessels involved limited access of antithrombic substances so that propagation of the thrombus often occurred Reactive endothelial proliferation apparently started promptly at the attachment of the thrombi and tended to encompass them The resulting lesions were most frequently seen at autopsy

This syndrome differs both clinically and pathologically from any of the well established disease entities but has been described by several authors notably Moschowitz and Baehr and his associates

↓ The following article is a critical analysis of the effects of splenectomy which contributes much to our understanding by separating the immediate and nonspecific effects on bleeding time and capillary fragility from the later and more specific effect on platelet levels —Ed

Idiopathic Thrombocytopenic Purpura H N Robson

(5) Quart J Med 18 79 97 October 1949

a rapidly progressive fatal course in which severe nonlocalizing mental and neurologic signs are prominent Tests of the clotting mechanism demonstrate increased bleeding time and defective clot retraction coagulation time is usually normal Capillary fragility is increased

At autopsy widespread purpura was present in all five cases appreciable splenomegaly was observed in three In other respects gross postmortem findings were nondescript

Platelet thrombi occluding capillaries and arterioles were the most striking microscopic features in all tissues examined



F g 87—Arte l n the s b t n e f th p n F al b dothel al c mul t f by l n h a t ng th p th omb t c l o R d c d f m × 395 (C t sy of Go e I Am J P th 26 155 175 Jan y 1950 f m A m d Fo c s Inst of P thology cc. n 113583)

Though the structure of thrombi could not be ascertained when they were compact and formed an amorphous or granular mass individual platelets could be seen in more loosely agglutinated portions Plugs of platelets obtained by centrifuging normal human blood presented similar morphologic features and staining reactions when they were fixed embedded and sectioned in the same fashion None of the venules appeared to be involved Though most lesions at autopsy were relatively recent there was usually a small number of organizing and organized occlusions which led to the inference that platelet thrombosing was episodic and that lesions occurred in crops

A paucity of platelet thrombi in lung capillaries and liver sinusoids was striking compared to their number in other tis

sues This seemed to be the reverse of what would be anticipated if the lesions were secondary to spontaneous agglutination in the circulating blood On the other hand when a section included an appreciable length of an involved vessel propagated platelet thrombi covered by a sleeve of hyperplastic endothelium were often observed The proliferating plump investing endothelial cells contrasted sharply with the flat tenuous lining of the occluded vessel and indicated an origin from a portion of the vessel not always in the plane of the tissue section Careful search revealed focal lesions of arterioles and capillaries on which platelet thrombi formed and from whence they grew along the length of the vessel

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Idiopathic Thrombocytopenic Purpura H N Robson[5]

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(5) Q J Med 18 279 297 Oct 1949

(Univ of Edinburgh) investigated 19 cases of idiopathic thrombocytopenic purpura with regard to changes in bleeding time capillary resistance and platelet counts before during and after splenectomy Similar observations were made on a control series of 13 patients on whom splenectomy was carried out for other conditions and 7 patients undergoing other abdominal operations Megakaryocytes in bone marrow were studied before and after operation

Splenectomy in cases of idiopathic thrombocytopenic purpura was associated with a sequence of changes in bleeding time capillary resistance and platelet counts Repeated observations made at short intervals during operation revealed that bleeding time began to decrease at or immediately after ligation of the splenic pedicle and continued to fall reaching normal levels 12 100 minutes from the time of initial skin incision Similarly capillary resistance improved reaching normal levels in 12 360 minutes and thereafter continued to increase so that after 1 192 hours a negative pressure of at least 500 mm Hg was usually necessary to produce one or more petechiae Platelet counts were altered much more slowly usually reaching normal levels in ½ 4 days Results of observations on control groups indicated that these changes were brought about initially by a nonspecific effect of operative interference followed by the effect of removal of the spleen

In 16 of the 19 cases recorded observations were made after discharge from the hospital at 3 months after splenectomy in most cases and again at varying periods from ½ to 14 years Fourteen of the 16 patients had remained clinically well despite the fact that only 6 showed entirely normal results in all three tests bleeding time capillary resistance and platelet count There was a considerable reversion to hematologic abnormality after the dramatic improvement immediately after splenectomy Yet bleeding recurred in only 2 of the 16 Of 12 patients tested three months after splenectomy 8 already showed one or more abnormal results by tests and no evident subsequent improvement On the other hand normal results achieved by the remaining four patients at the end of three months were sustained In idiopathic thrombocytopenic purpura final effects of splenectomy cannot be accurately assessed before three months after operation

There was no increase in primitive forms of megakaryocytes in bone marrow in cases of idiopathic thrombocytopenic purpura Platelet formation however was diminished and this was alleviated by removal of the spleen

It is suggested that the cause of idiopathic thrombocytopenic purpura lies in production by the spleen and other reticuloendothelial tissue of some factor which alters the state of capillaries and also reduces platelet formation from megakaryocytes Removal of the spleen may bring about a complete or partial reversal of these changes with consequent variation in clinical results

BAL Treatment of Thrombocytopenic Purpura Beneficial effect of BAL in treatment of poisoning by heavy metals (mercury lead copper gold) is now well established In such cases BAL is thought to compete with heavy metals for sulfhydryl groups with which the heavy metals combine to become active H Honkapohja[6] (Univ of Helsinki) reports a case in which blood complications due to gold therapy were treated with BAL

Man 53 was given sodium gold thiomalate for two months because of tender swelling of the distal interphalangeal joints After treatment he complained of continuous lassitude and three months later purpuric areas appeared on both thighs and bleeding from the gums occurred Platelet counts were 40 000 and 43 000 He was hospitalized with a diagnosis of thrombocytopenic purpura and osteoarthritis

BAL was given in doses of 1 7 cc every 4 hours for 48 hours then 1 7 cc twice daily for 7 days As soon as there was a decrease *in thrombocyte count BAL administration was resumed During* therapy gold excretion in urine increased 40 times and thrombocytes increased in number The tourniquet test progressively gave less positive results and bleeding phenomena ceased There were no manifest signs of BAL toxicity Total dosage was 74 8 cc The patient was followed for over six months and the number of thrombocytes remained over 100 000

COAGULATION DEFECTS

The first article by Soulier seems to us very important. Through comparison of the results of the prothrombin consumption test of Quick performed on the venous and capillary blood a convenient method of measuring effects due to tissue juice or tissue thromboplastin appears

(6) A med. *t Fenn e 38 33 37 1949*

to have been devised Recent studies by Tocantins likewise indicate a deficiency of such substances in hemophilic tissues thus perhaps for the first time permitting an understanding of the striking tendency to extensive bleeding into tissues in that disorder Other articles follow which, unfortunately for the clinical reader are necessarily concerned with various types of special laboratory studies However even if therapeutic progress is not outstanding significant knowledge concerning blood coagulation is coming from several clinics and laboratories We should like to pay tribute especially to the continuing contributions of Quick and his associates Over a period of years his instinct for physiologic analysis of the system with as little alteration as possible has yielded valuable results Progress has recently been powerfully aided by the use of silicone introduced by Jacques —Ed

Study of Prothrombin Consumption Practical Interest for Diagnosis of Hemorrhagic Diseases, Study of 89 Cases. For two years J P Soulier[7] (Paris) has been studying prothrombin consumption in every case of hemorrhagic disease under his observation The method used can be applied to serum from venous blood and from capillary blood The difference between the two serums is that capillary blood contains some admixture of tissue juice this addition of thromboplastin in physiologic amount increases prothrombin consumption Comparison of the two serums is useful for diagnosis

TECHNIC —Venous and capillary blood (0 5 ml) are obtained and kept for four hours in a water bath at 37 C then centrifuged to collect the serum To 0 1 ml undiluted serum is added 0 1 ml of standard thromboplastin and the mixture is incubated in the water bath for exactly 60 seconds This period is long enough for complete conversion of prothrombin and too short to permit the different antithrombic activities of serum to affect the clotting time. At the precise moment (60 seconds) 0 2 ml standard fibrinogen is added and clotting time recorded The method can be used in the same way on serum from clotted plasma results being parallel to those obtained with whole blood

Study of 17 normal subjects showed that normal prothrombin consumption time is over one minute for venous blood and over three minutes for capillary blood Study of 27 hemophiliacs revealed that prothrombin consumption times for venous or capillary blood or recalcified plasma were between four and six seconds and always less than eight seconds

Eight patients were referred with inaccurate diagnoses of hemophilia Three had hypoprothrombinemia as a result of dicumarol[8] intoxication Consumption time was over three minutes which was to be expected since the small amount of

(7) A ta med Sca d n 137 1 14 1950

prothrombin was entirely consumed during coagulation Prothrombin consumption was normal in four patients with Willebrand Jurgens syndromes (hereditary capillary defect with increased bleeding time normal platelets capillary resistance clot retraction and clotting time) One heparinized patient with a clotting time of 85 minutes had a consumption time of 72 seconds

In three patients with an anticoagulant in the circulating blood consumption time was as short as in hemophilia However prothrombin consumption in a mixture of pathologic and control plasmas was quite different In hemophilia normal plasma corrected the consumption deficit In the presence of an anticoagulant pathologic plasma affected consumption of normal plasma and the mixture behaved like hemophilic plasma

In 31 cases of *thrombopenia prothrombin consumption* was impaired This finding was remarkable since clotting time *did not reveal the profound disturbances of the first stage of* coagulation In all cases prothrombin consumption time in serum from venous blood was always below 18 seconds In serum from capillary blood consumption time was always longer and often as long as in normal blood In other words in thrombopenia prothrombin consumption is less defective than in hemophilia In capillary blood thromboplastin from tissue juice may more or less completely correct the deficiency observed in venous blood The prothrombin consumption defect appears to be as important as clot irretractability for ascertaining the presence of thrombopenia

Various other hemorrhagic syndromes were studied The prothrombin consumption time permitted division of these syndromes into a *group with abnormal consumption time and* one with normal consumption time thus permitting diagnosis of isolated vascular defect

Soulier concludes that prothrombin consumption time is a much more sensitive test than clotting time Normal clotting time is compatible with incomplete consumption of prothrombin It was previously known that plasma prothrombin must be reduced below 20 or 30 per cent for clotting time to be delayed It is now known that if 100 per cent of prothrombin is *present in* plasma clotting time is delayed *only* when less than 30 per cent of the prothrombin is consumed In hemo

philia in which prothrombin consumption is usually below 30 per cent for both venous and capillary blood clotting time is greatly delayed and hemorrhages are very severe since tissue juice cannot correct the defect In thrombocytopenia prothrombin consumption averages between 30 and 60 per cent Clotting time therefore remains within normal limits Because the clotting defect is more or less corrected by tissue juice spreading hematomas are not observed as in hemophilia but rather petechiae ecchymosis and mucous membrane hemorrhages due to the capillary fragility and nonformation of thrombus These studies suggest the possibility of making a correct diagnosis of hemophilia with capillary blood

Significance of Different Methods for Prothrombin Estimation and Their Relative Values are discussed by John H Olwin[8] (Univ of Illinois) The methods of estimating prothrombin are at present bioassays and to understand them knowledge of the mechanism of blood coagulation is essential Blood clots in two stages In the first stage prothrombin in the presence of thromboplastin prothrombin accelerator and calcium is converted to thrombin In the second stage thrombin converts fibrinogen to fibrin Variation in these and other factors may influence the normal physiologic clotting of blood

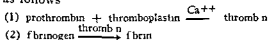
Methods used for measuring prothrombin are for the most part based on the so called one stage or two stage methods The one stage test is not a measure of prothrombin in that it leaves uncontrolled a number of factors other than prothrombin and allows the two phases of clotting to go on concurrently It is rather a measure of the over all clotting activity of blood under certain specific conditions It is a more accurate gauge of the likelihood of bleeding in a patient than is the two stage test From study of over 350 patients on dicumarol[9] therapy Olwin found that according to the one stage method plasma prothrombin may drop to below 10 per cent without evidence of bleeding Of these 350 patients 109 at one time or another during therapy had a prothrombin level below 10 per cent and of these only 35 had bleeding in some form Other factors may compensate for a prothrombin deficiency thus acting as a safeguard and this safety factor will be registered by the one stage test The two stage method on the other hand by controlling most of the coagulation and

(8) S g Gyn c & Ob t. 90 423 429 April 1950

anticoagulation factors and by taking into consideration the two stages by which blood clots is a more accurate measure of available prothrombin The chief objection to it is that it *is difficult to perform However once the required setup is* obtained performance is neither difficult nor excessively time consuming

Though it would seem to follow that the most accurate of the methods for estimating prothrombin would be the most valuable one in all instances this is not necessarily true In some cases the chief concern is whether or not bleeding will occur during or after surgery and in such cases the one stage method is a better estimate of the safety factor than is the two stage This is generally true in all conditions in which information is desired as to the likelihood of bleeding from prothrombin deficiency In conditions in which an accurate prothrombin estimate is important i e suspected liver damage the two stage method is preferable Olwin has found the one stage method more useful for control of heparin therapy For dicumarol[8] therapy since efforts are directed toward control of the single factor prothrombin the two stage method is the one of choice Understanding of what each method represents is of prime importance in selection of the particular test needed and in interpretation of results

Two Stage Procedure for Quantitative Determination of Prothrombin Concentration, with detailed directions for preparation of reagents is described by Arnold G Ware and Walter H Seegers[9] (Wayne Univ) The only known way to identify prothrombin is to convert it to thrombin which is readily recognized by its property of changing fibrinogen to fibrin Equations for the reactions involved are generally written as follows



(1) prothrombin + thromboplastin $\xrightarrow{Ca^{++}}$ thromb n

(2) f brinogen $\xrightarrow{\text{thromb n}}$ f brin

When estimating prothrombin by two stage methods these reactions are completed one at a time Conversion of prothrombin to thrombin is first allowed to take place and then the second reaction is utilized to measure the amount of thrombin formed

It is now generally accepted that there is a factor in nor

(9) *Am J Cl P th 19 471 48 M y 1949*

mal plasma other than prothrombin or thromboplastin which affects the first reaction of clotting The authors refer to this factor by the term Ac globulin (accelerator globulin) Quantity of Ac globulin normally found in human plasma is sufficient to provide a maximal thrombin yield in analyses for prothrombin by the two stage procedure However if the amount of Ac globulin is much below normal the two stage analysis may indicate a false low prothrombin titer For this reason it has been necessary to modify the two stage method in order to assure a maximal yield of thrombin when Ac globulin is low or absent This is done simply by supplying an adequate amount of Ac globulin during the analytic procedure Diluted bovine serum fresh or carefully preserved in the cold is used for this purpose With this modification the two stage method is believed to measure prothrombin specifically and accurately

With use of human plasma deficient in Ac globulin it has been shown that there is a correlation between Ac globulin concentration and apparent prothrombin concentration as determined by the original two stage technic It is thus possible to estimate Ac globulin content of human plasma by comparison of prothrombin titers obtained by the modified and the original two stage technics The modified prothrombin analysis gives the true prothrombin titer the original two stage procedure gives low prothrombin values which are proportional to the Ac globulin deficiency of the plasma

Prothrombin Consumption Test Its Clinical and Theoretical Implications are discussed by Armand J Quick and Jean E Favre Gilly[1] (Marquette Univ) The prothrombin consumption test is based on the principle that by determining prothrombin before and after coagulation is complete a measure of plasma thromboplastin that reacts with prothrombin is obtained In the original test blood was allowed to remain one hour at 37 C after coagulation before prothrombin of serum was determined Occasional inconsistencies in results were encountered and in searching for the cause of these it was found that when normal blood clots in a test tube all fibrinogen is converted to fibrin before a detectable diminution of prothrombin occurs This leads to the logical conclusion that the fibrin clot being uniformly dispersed through

(1) Blood 4 1 81 1289 Decembe 1949

the mass of blood presents an enormous adsorbing surface which quickly and effectively removes nascent thrombin and thereby prevents sufficient accumulation to initiate the chain reaction that is mediated through the labilizing action of thrombin on platelets Almost all consumption of prothrombin therefore occurs only after serum has been separated from the clot either mechanically by centrifugation or spontaneously through clot retraction

As a result of the observation that prothrombin consumption is decidedly influenced by separation of serum from clot the original test was modified in order to control the adsorption factor of fibrin Instead of waiting one hour after coagulation before determining prothrombin of the serum eight test tubes each containing 2 cc blood were allowed to coagulate Every 15 minutes two tubes were centrifuged to one of which 0 1 cc of 0 4 M sodium citrate was added and prothrombin of the serum was determined at once and after three 15 minute intervals on each tube Since conversion of prothrombin is rapid immediately following the break in the intimate contact of the serum with the fibrin reticulum thrombin forms and accumulates during centrifugation therefore the prothrombin time done directly is abnormally short since it measures thrombin already present plus the amount formed during the test The latter increments can be prevented by adding sodium citrate to the clotted blood just before centrifugation so that thrombin formation is stopped and a true prothrombin value in serum is obtained

Prothrombin consumption varies considerably in normal persons In hemophilia and in thrombocytopenia it is very incomplete In hypoprothrombinemia the prothrombin may be very complete as in congenital hypoprothrombinemia of the component A deficiency type or surprisingly incomplete as in dicumarol® hypoprothrombinemia

The most remarkable finding is that in the test tube only a minute amount of prothrombin is converted to thrombin in coagulation of all the fibrinogen of the blood Only after separation of serum from the clot does prothrombin begin to decrease rapidly Obviously fibrin itself is the most important physiologic antithrombin Previously it was difficult to explain how this powerful latent clotting capacity of blood was held in check It is now clear that the strong adsorptive

property of fibrin not only guards against accumulation of thrombin but also prevents the autocatalytic reaction involving labilization of platelets by thrombin from being set in motion except at the site of vascular injury

Concentration of Component A in Blood, Its Assay and Relation to Labile Factor For clinical purposes it is advantageous to divide the clotting factors required for formation of thrombin into two categories thromboplastin formers and constituents of the prothrombin complex The latter are essential for prothrombin activity as measured by the one stage prothrombin time determination According to Quick agents in the prothrombin complex are labile factor components A and B and bound calcium The labile factor is characterized by its instability especially in decalcified plasma and its nonadsorbability by tricalcium phosphate Component A is the principle which is adsorbable by tricalcium phosphate requires vitamin K for its synthesis [is probably inactivated by sodium citrate —Ed] and is deficient in one type of congenital hypoprothrombinemia It is probably this component which is generally called prothrombin by other investigators Component B is difficult to define Its existence is postulated to explain a second type of congenital hypoprothrombinemia which is also hereditary and in which the labile factor and component A appear to be normal [Elsewhere Quick and Stefanini have presented evidence that prothrombin B is concerned with the conversion of prothrombin A from an inactive to an active form —Ed]

Desirability of having methods for quantitative estimation of the various constituents of the prothrombin complex is obvious Recently a procedure has been developed for estimating concentration of the labile factor and in the present report Armand J Quick and Mario Stefanini (Marquette Univ) describe experiments which not only yield a procedure for estimation of component A but also furnish results which show its relationship to the labile factor The one stage method for prothrombin time determination was used

When normal oxalated plasma was added in progressively increasing amounts to plasma from which component A of prothrombin was absent or very low owing to vitamin K deficiency removal by adsorption with tricalcium phosphate

(2) J Lab & Clin Med 34 973 982 July 1949

or congenital lack prothrombin time was characteristically decreased until approximately one volume was added to one volume of the defective plasma After this prothrombin time became the same as that of normal plasma This indicated that normal plasma supplies about twice as much component A as is required to attain a normal prothrombin time and that therefore component A is apparently not the specific determinant of prothrombin time even in the presence of an excess of labile factor Prothrombin time as determined by the one *stage procedure therefore does not measure any particular* constituent of the prothrombin complex but rather their com*posite effect*

Amount of component A can be determined as follows By means of adsorbing oxalated plasma with tricalcium phosphate and treating the latter with sodium citrate an eluate is obtained which contains almost all of the component A present in plasma When this eluate is added in an amount equivalent to that in the volume of normal plasma from which it was obtained to plasma lacking component A normal prothrombin time is restored By adding progressively decreasing amounts of the eluate to component A free plasma a series of values of prothrombin time are obtained which correspond well with the original prothrombin curve Component A is active only if an adequate amount of labile factor is present

When this method for quantitative estimation of component A was used the concentration of component A in plasma of a patient with congenital hypoprothrombinemia was shown to be deficient Eluate obtained from his plasma when tested for component A potency either on normal calcium *phosphate plasma or on his own plasma yielded the same* low result whereas eluate from normal human plasma restored his prothrombin level to normal exactly as it did in normal calcium phosphate plasma

When severe *hypoprothrombinemia* was *produced* in chicks by means of a vitamin K free diet for 10 days an eluate of *the plasma of these chicks showed no prothrombin* potency when tested on hen tricalcium phosphate adsorbed plasma *indicating a complete lack of component A It is log*ical to conclude therefore that deficiency of vitamin K produces a *pure component A type of hypoprothrombinemia*

Similarly in dogs hypoprothrombinemia resulting from dicumarol® could be promptly and completely corrected by addition of a concentrated solution of component A i e the eluate from tricalcium phosphate adsorbed plasma thus indicating that the basic defect in dicumarol® poisoning is also lack of component A

Parahemophilia (Owren) New Form of Hemorrhagic Diathesis E Frank N Bilhan and H Ekren[3] (Univ of Istanbul) describe a case

Man 29 had bled profusely on many occasions one epistaxis lasting 48 hours One brother had died of hemorrhage in infancy and the father was subject to abnormal bleeding In 1947 the patient had a sudden attack of hematuria unassociated with colic which continued intermittently for six months A second attack was accompanied by pain but no stone was found During the last attack in 1948 hematuria was accompanied by pain and x rays showed a kidney stone The urologist who advised nephrotomy requested a study of the patient s hemorrhagic diathesis to determine whether operation would be dangerous because of bleeding

Pseudohemophilia and true hemophilia were ruled out because there had never been petechiae ecchymoses or hemarthroses Blood platelets numbered 344 000 and bleeding time was six minutes Coagulation time was normal but the clot was not firm In repeated tests by Quick s method prothrombin time was 47 seconds When prothrombin time was 47 50 seconds the patient did not bleed but when it reached 60 80 he bled profusely The assumption that bleeding was caused by reduced prothrombin was untenable because vitamin K administered for 12 days had no effect Whole blood transfusions shortened prothrombin time immediately and for eight hours During an acute attack of hematuria with high fever prothrombin time reached 80 seconds but response to transfusion was immediately favorable and the operation performed without unusual bleeding

Tests were carried out to determine whether human or animal plasma free from prothrombin or a factor isolated from such plasma influences prothrombin time When the patient s plasma was diluted to one third its strength with salt solution prothrombin time was reduced to 45 seconds when calves plasma was used it reached a low of 40 seconds Prothrombin free normal plasma or its active principle according to Owren was obtained by precipitation with dilute acetic acid and dissolved after an hour in physiologic saline Either invariably reduced prothrombin time to 19 seconds The patient s plasma shortened the coagulation time of a true

(3) Acta haematol. 3 68 90 1950

hemophilic Owren s factor from the hemophiliac s plasma shortened the prothrombin time of the patient described

The authors state that this case and one reported by Owren are identical and they adopt the term parahemophilia proposed by Owren A plasma factor was absent in both cases which was not related to the thromboplastin but to the pro thrombin complex Three cases of idiopathic hypoprothrom binemia in the literature may belong in the category of para hemophilia It is recommended that future cases be studied from the viewpoint of the plasma factor

Hypoprothrombinemia Studies of Case of Idiopathic Type and Effect of Serum Administration are reported by Charles L Crockett Jr Donald Shotton Charles G Craddock Jr and Byrd S Leavell[4] (Univ of Virginia)

Girl 5 was hospitalized for study of abnormal bleeding which had occurred intermittently since age 2 weeks Episodes of severe epistaxis hematemesis and melena had occurred but there was no history of hemarthrosis Hematuria was present on admission No history of hemorrhagic phenomena in other members of the family could be elicited from the mother Prothrombin conversion time of the mother s plasma was normal

Examination revealed many old hematomas but no jaundice adenopathy or hepatosplenomegaly Laboratory studies revealed 3 700 000 red cells 11 Gm hemoglobin 7 200 white cells normal blood and bone marrow differential counts 1 3 per cent reticu locytes hematocrit 39 sedimentation rate 6 mm in 1 hour 388 000 platelets bleeding time of 2½ minutes negative tourni quet test and normal clot retraction Prothrombin time ranged from 62 to 92 seconds and clotting time from 11 to 48 min utes Liver function studies were within normal limits Electro phoretic study of the blood revealed a normal protein pattern with no fibrinogen deficiency Direct examination of nail bed capillaries revealed normal appearance and normal re ponse to traumatic rup ture Lack of response to large doses of synthetic vitamin K prepara tions seemed to exclude vitamin K deficiency Therefore it appeared that this patient had idiopathic hypoprothrombinemia Absence of any change in either subjective or objective clinical manifestations including signs of liver disease over three years of repeated observa tions substantiated this interpretation

Repeated mixture of normal plasma with the patient s plasma in equal amounts substantially lowered the prothrom bin time but not to normal levels Existence of a factor in normal blood which is necessary for rapid conversion of pro thrombin seems beyond dispute There seemed little doubt

(4) Blood 4 1298 1309 D mb 1949

that normal serum possessed a factor which was capable of accelerating prothrombin conversion in this patient's plasma This factor or factors has been called Ac globulin After the in vitro demonstration of a deficiency of Ac globulin in the patient's blood it was possible to bring about a decided reduction in the prothrombin time by intravenous administration of relatively small amounts (15 45 cc) of fresh normal (thrombin free) serum A further reduction of prothrombin time to near normal values was brought about by combined whole blood and serum administration Evidence suggested that partial correction of both prothrombin and Ac globulin deficiency resulted from such therapy

These studies support the concept that serum contains an active substance which is capable of accelerating prothrombin conversion to thrombin Deficiency of this substance may play a role in many types of hemorrhagic states It is probable that alterations of Ac globulin are of particular importance in various types of prothrombin deficiency

Coagulation Defect in Hemophilia with Particular Reference to Conversion of Prothrombin to Thrombin and Evolution of Prothrombin Conversion Accelerator Most investigators agree that conversion of prothrombin to thrombin is retarded in coagulation of hemophilic blood This is reflected in the high prothrombin activity of hemophilic serum Clotting of hemophilic blood can be accelerated by addition of thromboplastin normal plasma or fractions thereof Recently substances have been described which arising in blood during coagulation accelerate conversion of prothrombin to thrombin in presence of thromboplastin plus calcium Benjamin Alexander and Andre de Vries[5] (Boston) present data indicating that in the elaboration of one of these clotting factors serum prothrombin conversion accelerator (SPCA) also the coagulation of hemophilic blood is abnormal

Prothrombin activities of serums removed and oxalated one hour after coagulation from hemophilic blood were abnormally high Conversely SPCA activities were abnormally low No correlation was evident between coagulation time and these serum entities

In normal subjects accelerating coagulation by addition of thromboplastin increased SPCA and removed the last

(5) Blood 4 752 58 June 1949

traces of serum prothrombin activity Restoring clotting time of hemophilic blood to normal in vitro by addition of small amounts of thromboplastin failed to lower residual serum prothrombin activity appreciably SPCA concentration was also unaffected When however larger amounts of thrombo plastin were supplied both prothrombin consumption and SPCA evolution were sometime greatly increased attaining normal values It is striking however that in two subjects substantial amounts of serum prothrombin activity were still demonstrable although the parent blood had clotted in 180 seconds or less This is in marked contrast to what was ob served in normal subjects

Restoration of clotting time of hemophilic blood toward normal by in vitro or in vivo addition of normal plasma de creased residual serum prothrombin activity substantially in some cases but activity rarely reached normal values SPCA however rose only slightly even when as much as 700 cc normal plasma was infused Addition of normal serum con taining substantial SPCA activity to hemophilic blood accel erated coagulation only slightly as compared with the clot promoting effect of the parent plasma

Hemophilic plasma and serums obtained one hour after coagulation were subjected to simultaneous prothrombin de termination by both one stage and two stage technics Whereas by the one stage procedure serum prothrombin ac tivity was no less than that of its parent plasma by the two stage method it was markedly less

Superiority of Vitamin K_1 Oxide over Menadione Sodium Bisulfite U S P and Synkayvite® in Reversing Dicumarol® Hypoprothrombinemia To establish a broader clinical basis for control of dicumarol® effect David F James Ivan L Ben nett Jr Peritz Scheinberg and John J Butler[6] (Atlanta Ga) administered menadione sodium bisulfite synkayvite® and vitamin K_1 oxide in large single doses to patients with hypo prothrombinemia induced by dicumarol® Efficiency of these substances was estimated on the basis of time elapsing be tween administration of the drug and conversion of pro nounced to moderate hypoprothrombinemia and time elapsing after administration of the agent until appearance of a pro thrombin level consistent with intravascular clotting

(6) A h I t M d 83 63 65 J 1949

Vitamin K_1 oxide was most effective in both respects For 26 patients given 0 5 Gm or more intravenously prothrombin time arrived and stayed at a level lower than that of 30 per cent normal plasma in an average of 13 hours When menadione sodium bisulfite (64 180 mg) was given intravenously to 19 patients this shortening of prothrombin time was achieved in an average of 4 7 days When synkayvite* (100-500 mg) was given intravenously to six patients an average of 5 3 days elapsed Six patients with severe hypoprothrombinemia treated with 0 1 Gm or more of vitamin K_1 oxide required an average of four hours to achieve a prothrombin concentration within what is generally regarded as a safe range In patients who have recently been given vitamin K_1 oxide the amount of dicumarol* needed again to prolong prothrombin time to beyond that of 20 per cent normal plasma is unchanged if menadione sodium bisulfite has recently been given but with vitamin K_1 oxide the amount of dicumarol* must be increased threefold

Analysis of the time required for achievement of dicumarol* effect in 101 patients showed that in about 1 of every 5 five or more days was necessary for a significant therapeutic effect with dicumarol* in the usual doses (300 mg the first day and 200 mg on each successive day) The authors data suggest that on the basis of the amount of dicumarol* needed by a given patient it is possible to predict how much may be necessary during a second course in the near future Five patients who were allowed to recover untreated from the effect of dicumarol* were treated a second time after at least two days during which prothrombin time was equal to that of normal plasma During the second course of dicumarol* requirements varied from the first course by no more than two doses Analysis of normal control values in a large number of determinations revealed their variability and the necessity therefore of using several controls if a proper dilution curve for prothrombin is to be derived

[This striking activity of vitamin K_1 oxide confirms earlier observations by Davidson Aggeler and others According to Jacques vitamin K acts by progressive displacement of dicumarol* from the liver For this reason perhaps the more slowly metabolized vitamin K oxide is more effective than other forms of vitamin K—Ed]

THE HEART *and* BLOOD VESSELS *and* THE KIDNEY

TINSLEY R. HARRISON M.D.

PART IV

THE HEART AND BLOOD VESSELS AND THE KIDNEY

PROGRESS IN THE CARDIOVASCULAR FIELD *DURING THE LAST DECADE*

The medical historian of the future will probably state that more progress occurred in the 1940 s than in any previous pe riod of similar length He will consider as especially significant the better understanding that has developed of the psychologic impact of heart disease on the patient and the family and the realization that in a patient with complaints referable to the heart the physician s first duty is to alleviate fear regardless of whether *or not the structural disease exists He would also deem* especially important the fact that in this decade occurred the beginnings of a clear scientific rationale for more intelligent recommendation of rest versus activity and of the value and harm of the various postures These advances affect all types of heart disease and hence are particularly notable

Another basic principle which emerged during this decade followed the introduction by William Dock of the concept that senile deterioration of the myocardium occurs independently of *coronary arteriosclerosis This involutionary change appears to* be a least common denominator in almost all heart failure in patients over age 50 regardless of the apparent primary disease process The concept explains the frequency of heart failure in elderly persons with hypertension various valvular diseases thyrotoxicosis etc and the rarity of heart failure in younger persons (in the absence of active myocarditis) despite the pres ence of similar disorders

Instrumental Methods and Procedures

The usual history of new instruments is that of their initial use as research tools plus the gradually increasing clinical application as advantages and limitations become clarified The

striking advance in electrocardiography after the introduction of the precordial leads in the thirties was followed in the forties by the general introduction into clinical practice of the V leads and the unipolar limb leads The angiocardiographic procedure has demonstrated its usefulness in the diagnosis of congenital lesions It is not without risk and should be utilized only by those experienced with the method

The catheterization technic was perfected and its value as a research tool was demonstrated The greatest practical value of the procedure thus far has been in the differentiation of the various types of cyanotic congenital cardiac disease thereby improving the criteria for selection of patients suitable for the Blalock Taussig operation

Ballistocardiography a purely research method in the thirties emerged as a clinical procedure in the forties when its value in early diagnosis of coronary disease began to be apparent

To those interested in hemodynamics the most exciting development was the introduction of the electrokymograph Here at last was a tool which allowed the investigator to study the Starling curve in man Thus the basic physiology of the heart could be studied at the bedside The prediction may be ventured that the electrokymograph or some modification of it will eventually be the first tool to threaten the supremacy of the eye the hand and the ear in diagnosis of cardiac disease and the supremacy of the history in evaluation of the functional capacity of the myocardium

DISEASES OF THE HEART

Congestive heart failure—During the early part of the decade the importance of disturbed renal function became apparent and it was at first thought that the demonstration of the importance of sodium retention by the kidney necessitated discarding the previously accepted ideas of Starling s concept of cardiac edema Toward the end of the decade it began to be recognized that the new advances while of great significance were additive rather than substitutive and that the concept of the 1930 s (and indeed of the previous century) that the basic mechanism of heart failure was elevation of pressure in the chambers of the heart was still valid Nevertheless the practical importance of the secondary renal factors and of the secondary increase in blood volume became evident

In the treatment of heart failure the outstanding advances

were the more rational use of digitalis following the development of purified products the general recognition both of the value of sodium restriction and of its harm when carried to excess and practical and theoretical advances with regard to the mercurial diuretic Especially significant was the reduction of the hazard of pulmonary infarction through development of improved methods of diagnosis and management of thromboembolic disease

Congenital heart disease —The most dramatic developments were those in surgical treatment In the late thirties operative treatment of certain noncyanotic types of congenital heart disease was begun and during the forties it was demonstrated that both patent ductus arteriosus and coarctation of the aorta were curable These operative procedures when carried out by surgeons with proper experience are attended by comparatively low mortality Those patients with congenital disorders associated with restriction of pulmonary blood flow and with right to left shunts were found to be strikingly benefited by the Blalock Taussig procedure Although complete cure cannot be achieved invalidism has been overcome and when considered in relation to the usually precarious preoperative state the mortality rate has been gratifyingly low and is declining steadily

The development of successful surgical treatment was strong stimulus to improvement in diagnostic methods The consequent developments in the angiocardiographic and catheterization technics have been cited

The study of the relationship between maternal rubella during pregnancy and the subsequent birth of a child with a congenital disorder of the heart opened for the first time the door to prevention

Rheumatic heart disease —The most important development in rheumatic heart disease occurred late in the decade when cortisone and ACTH began to be used The dramatic control of the disease with these compounds justified the hope for a truly successful therapy However long range follow up studies are needed before these new methods can be finally evaluated

The case for sulfonamide prophylaxis was just being established when penicillin prophylaxis began to be advocated Pending long range investigations it would appear that the latter procedure will be the method of the future

Another notable step was the firm establishment of the hemo-

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In the treatment of heart failure the outstanding advances

(and other) arteries seems indisputable Less convincing but still intriguing is the idea that the normal values for blood cholesterol in the American population represent hypercholesteremia and that atheroma is less common in subjects with levels in the lower portion of the normal range The relative importance of intake synthesis excretion and destruction as determinants of the blood level remains in dispute The demonstration that cholesterol may be synthesized from 2 carbon fragments was of great importance and offers the first rational explanation for the increased tendency of obese subjects to develop atherosclerosis Since fat is oxidized by progressive splitting of 2 carbon fragments and since the Schoenheimer concept of dynamic equilibrium indicates that the fat depots are metabolically active rather than passive it is altogether probable that the total fraction of potential precursors of cholesterol available in the metabolic pool at a given moment is increased in obese subjects *Thus the rationale for thinness as a means of preventing atherosclerosis* appears to be established Less convincing is the concept of the specific importance of cholesterol restriction Pending further knowledge it would seem desirable to ascribe first importance to total caloric restriction second significance to restriction of fat (both mineral and vegetable) and third place to restriction of cholesterol per se

Strong evidence for the concept that the tendency to atheroma may be related not only to the quantity of fat but also to the quality—i e the state regarding dispersion and particle size—has recently been presented

Advances specifically outstanding in the management of coronary disease include those in the field of thromboembolism and the increasing evidence that nitroglycerin may perhaps have a curative (by widening collateral channels) as well as a symptomatic effect in persons with myocardial anoxia

The great practical gains resulting from the application of Frank N Wilson s basic principles to clinical electrocardiography are so well known as to require no further comment

Peripheral vascular disease —Here the advances were rapid Better means of recognizing peripheral thrombosis in its early stages were developed Anticoagulant therapy—a matter largely of theoretical interest in 1940—was made practical and its value was established by well controlled studies The importance of femoral ligation was demonstrated although the precise

lytic streptococcus as the most important (if perhaps not the sole) initiating agent The concept of the disturbed antigen antibody mechanism of the disease appears to rest on firm ground The importance of the various spreading factors involved in the hyaluronidase enzyme system would appear to have been demonstrated The relationship of the salicylates and allied substances to these factors has been shown and represents a promising avenue for further research

Bacterial endocarditis—Here is the most brilliant of all the practical advances The reduction in mortality from practically 100 per cent to less than 20 per cent in this fell disease as the result of antibiotic therapy requires no comment

Diseases of Blood Vessels

Hypertension—At the beginning of the decade an objective observer would probably have predicted that the rapid progress in knowledge of hypertension during the thirties would yield handsome returns in the forties This optimistic hope has not been justified The relative importance of renal pressor substances renal homeostatic mechanisms tending to prevent hypertension neurogenic and psychic factors endocrine disorders and unknown mechanisms remains obscure

The case for sodium restriction seems to be established for some patients but it is equally clear that this procedure has little or no value in most patients It seems that the beneficial effects sometimes obtained from the rice diet are chiefly but perhaps not entirely the result of the low sodium content of the diet The possible significance of the paucity of protein of cholesterol and of allergens in this diet is uncertain There is no evidence that rice as such has a positive value

The various types of surgical sympathectomy have been shown to be useful in delaying the progress of the disease in properly selected subjects It is as yet too early to predict whether or not the sympatholytic drugs will ever replace the operative procedures The results with veratrine compounds are of interest but their long range usefulness remains to be defined

Atherosclerosis—Although practical advances were limited theoretical knowledge increased at a rapid rate For the first time an attitude of optimism toward the future seems justified

The evidence that hypercholesteremia however induced favors the production of atheromatous changes in the coronary

to renal hypertension was not realized although advances were made the progress was disappointing

To the philosopher (or in the present instance the pseudo philosopher) certain conclusions seem to emerge from this brief survey of the rapid progress made in the cardiovascular field during the past decade The first is that few problems in medicine are inherently insoluble If the problem of bacterial endocarditis can be largely solved if blue babies can live to be come pink adults if persons with congestive failure can be kept alive for many years and often for decades if an optimistic view point toward the probable future developments in atherosclerosis has emerged it would be folly to believe that disorders which *now seem totally hopeless will remain so*

The second conclusion is that the sharp lines between the ivory tower of research and the practical care of the patient are becoming blurred Fundamental advances in physics and chem istry are soon followed by better understanding of the mecha nisms of disease the result is the trial of new therapeutic pro cedures These procedures often require extensive clinical study by persons skilled in the scientific method before they can safely be utilized by physicians living at a distance from the best laboratories The public is on the one hand entitled to receive promptly the benefits of new discoveries without on the other hand suffering the risk of being victims of uncritical evaluation of untried remedies The medical profession is entitled to derive the satisfaction which comes from doing a first class job with its patients and from being in the forefront of intellectual advance Such satisfaction can be achieved only if physicians have free dom of action and independence of thought It is doubtful whether these conditions can be realized except through some plan which brings medical research and medical education closer to the profession To develop such a plan will require the exercise of wisdom and patience on the part of the profession the medical schools and the public

—Tinsley R Harrison

indications for this procedure rather than for anticoagulant therapy alone are still debated

The importance of surgical and chemical sympathetic block was demonstrated both for arterial and venous obstruction Whether the sympatholytic drugs will ever replace sympathec tomy is uncertain The drugs may be more valuable when a generalized effect is desired as in certain persons with hyper tension but surgical sympathectomy will probably remain the method of choice for the treatment of local vascular disorders unless an agent with long duration of action (weeks or months) can be developed for local injection

New technics for more precise study of local circulation were developed Those employing isotopes would seem to offer the greatest long range promise

Cerebral vascular disease —In this most neglected of all the important fields of medicine practical progress was almost nil The biochemists have begun to clarify a few of the mysteries concerning cerebral enzyme systems and a few individuals in the field of physical medicine continue to make valiant efforts Despite the paucity of practical advances the development of methods for studying cerebral blood flow and the metabolism of the intact human brain may be expected to lead to eventual therapeutic progress

Disorders of the Kidneys

The great advances were in the research field and resulted from the application of the technics and principles of Homer Smith to the study of disease It can be predicted that the infor mation so gained will be followed by important advances in treatment during the 1950 s

Other important advances included the growing evidence that acute glomerulonephritis is fundamentally a disorder of antigen antibody mechanisms the realization that renal con servation of solutes is equally as important as renal excretion of solutes in the fundamental homeostatic role of the kidneys the clear delineation of the concept of the fulminating nephroses (lower nephron nephrosis) and the gradual extension of knowl edge of the metabolic role of the kidneys

The old problem of the artificial kidney was attacked anew and may be approaching solution.

As already indicated the expected rate of advance in regard

and frequently in lead II and inversion of T_3 and eventually T Pulmonary diseases which cause cor pulmonale i e right ventricular strain depress the diaphragm and cause the heart to be vertically placed so that it is difficult to know whether changes in the ECG are due to right ventricular strain or to a vertical position of the heart Precordial leads are of some help in establishing diagnosis of right ventricular hyper trophy Whereas normally in V R is very small and S is deep and in V R is tall and S is small in right ventricular hypertrophy the reverse may be true

In children and in young adults widening and notching of the P waves are a reliable indication of auricular enlargement but in older persons such changes occur commonly and are not diagnostically significant Though QRS widening is fre quently encountered in association with long standing and ad vanced left ventricular enlargement it is due only in slight part directly to increased thickness of the myocardium

The simplest and one of the most useful measurements of heart size in x ray examination is the transverse diameter Assumption that the transverse diameter should be less than half the transverse diameter of the chest at the level of the diaphragm has been widely popularized but is crude and in exact More accurate standards based on weight and height have been established Diameters more than 10 per cent above the predicted value should be regarded as abnormal Two other diameters the long and broad are well known The long diameter extends from junction of the cardiac and vas cular silhouette on the upper part of the right border of the heart obliquely down to the apex on the left This diameter which is approximately 10 per cent greater than the transverse diameter is increased chiefly as a result of left ventricular enlargement The broad diameter is the greatest single diam eter from upper left to lower right heart border perpendicular to the long diameter These two diameters are of interest chiefly for their product the frontal cardiac area which is an expression of the two dimensional size of the cardiac shadow

Measurement of aortic caliber is difficult The left border of the descending aortic arch is visualized in frontal x rays and if the esophagus is filled with barium the right border of the aorta is indicated by the aortic indentation of the

The articles in this chapter emphasize the importance of the simple clinical tools and particularly the information to be gained by physical examination of the heart In occasional instances electrocardiographic study is essential with regard to arrhythmias and in many instances this method is of great value in the interpretation of chest pain When the cardiac impulse cannot be felt radiographic examination may be invaluable in determining cardiac size In deciding what type of congenital heart disease is present elaborate special studies by angiocardiography and catheterization may be necessary But in most patients with cardiac disease the history and physical examination yield all the essential information and often this information cannot be obtained by any other means Thus in the final analysis diagnosis of acute pericarditis depends on the characteristic friction sounds whereas that of valvular disease depends on the interpretation of murmurs The patient s story remains the supreme court with regard to the functional integrity of the myocardium and of the coronary circulation The interest in special methods of examination should never replace the physician s desire to perfect himself in those older technics which remain the backbone of diagnosis —Ed

Cardiac Enlargement is discussed by Harry E Ungerleider[1] (Equitable Life Assurance Soc New York City) Hypertrophy and dilatation as a rule are closely associated but are detected by different diagnostic technics hypertrophy by electrocardiograms dilatation by x rays Changes may occur in shape if not in size of the heart which suggest hypertrophy such as rounding of the left ventricular contour in concentric left ventricular hypertrophy and elevation of the cardiac apex in right ventricular hypertrophy producing the *coeur en sabot* Enlargement seen in x rays means dilatation of cardiac chambers however

Left ventricular hypertrophy may be considered to exist when left axis deviation occurs in association with any of the following changes in the ECG amplitude of QRS (sum of R_1 and S_3) exceeding 2 5 millivolts or R wave in lead I over 15 mm depression of S T segment in lead I or lowering of T_1 below 1 mm Increased amplitude of QRS may be attributed to increased mass of left ventricular musculature S T segment and T wave changes are due to relative ischemia of the deeper layers of the left ventricle

Pattern of the ECG in right ventricular hypertrophy consists of right axis deviation plus S T depression in lead III

(1) Am. Pract. 1 286 298 M h 1950

for a patient to have a complete cardiac work up with x rays and electrocardiograms when careful auscultation would have quickly revealed the nature of the disorder and might have resulted in a more accurate diagnosis because of observations overlooked or misinterpreted by other methods

Auscultation of the heart enables one to eliminate certain diagnoses e g if no murmurs whatever are heard even with the patient turned to the left lateral position or sitting upright subacute bacterial endocarditis or chronic rheumatic valvular heart disease can be eliminated fairly safely A more important contribution of auscultation is the establishment of a definite diagnosis by detecting certain abnormal sounds Pericardial friction almost invariably indicates acute pericarditis In most cases an apical rumbling murmur diastolic or presystolic in time is diagnostic of mitral stenosis With familiarity of the character of this murmur diagnosis is certain even if the murmur is faint or present only after effort or heard when the patient is lying on his left side This is also true of a faint early diastolic murmur at the base of the heart in the diagnosis of early aortic insufficiency It is not to be inferred that detection of cardiac murmurs always leads to a decisive diagnosis there are many instances especially when systolic murmurs are involved in which proper evaluation may be most difficult This does not detract from the value of auscultation but rather presents an additional challenge to analyze physical observations correctly

Another type of information derived from auscultation is what might be called clues to diagnosis The heart of a patient stricken with severe epigastric pain resembling acute pancreatitis or perforated peptic ulcer may show a classic diastolic gallop A snapping first sound while the heart rate is rapid and grossly irregular in the absence of any murmurs frequently indicates mitral stenosis in such a case

Apart from the evidence of valvular and pericardial disease which may be obtained by simple auscultation detection of arrhythmias or changes in quality of heart sounds is important Tripling of sounds (a gallop rhythm) is overlooked too frequently When the extra or third sound of a gallop can be identified as occurring in diastole it almost always indicates grave heart disease however it is not sufficiently appreciated that gallops in which the extra sound occurs during

esophagus therefore the diameter at this level can be ascer tained by subtracting 2 mm representing the thickness of the esophageal wall This method is not dependable when the aorta is tortuous and the aortic knob projects to the left Where a portion of the aortic knob is indistinct true diameter of the aorta at this level may be ascertained by completing the circle of which the aortic knob is an arc by means of a compass Diameter of the aorta at this level varies from 2 to 4 cm The table established for predicting transverse diam eter of the heart from weight and height may be used equally well for the aortic arch diameter An aorta may be consid ered abnormal if the diameter exceeds the predicted value by 15 per cent

Configuration of the enlarged left ventricle varies some what depending on whether hypertrophy or dilatation pre dominates In hypertrophy as in early hypertension it be comes increasingly convex Enlargement of the left ventricle downward laterally and posteriorly is seen particularly in aortic insufficiency where dilatation of the left ventricular cavity predominates the diastolic volume necessarily being large because of increased systolic output Posterior enlarge ment of the left ventricle is best evaluated on fluoroscopy in the left anterior oblique position When enlargement is pro nounced the left ventricular border which ordinarily clears the anterior border of the spine at an angle not greater than 60 degrees may not clear the spine at all

The right ventricle does not participate in forming the cardiac contour in the posteroanterior projection since it forms the anterior surface of the heart Nevertheless enlarge ment of this chamber may be indicated indirectly by its dis placement of the right auricle to the right which causes in creased prominence and convexity of the right border Even more characteristic is a straightening and increased promi nence of the upper left heart border between the aortic arch and the left ventricular segment resulting from elevation and rotation of the pulmonary artery by the enlarged outflow tract or infundibular portion of the right ventricle The right ven tricle is best studied in oblique views as is the left atrium

Diagnostic Value of Cardiac Auscultation is emphasized by Samuel A Levine[2] (Boston) It is not uncommon today

( ) J A M A 141 589 593 Oct. 29 1949

mal as indicative of a so called weak heart muscle Abnor malities in the first heart sound (like other auscultatory phenomena) will not be detected unless they are specifically listened for

These are but a few examples of auscultatory observations which can readily be made with a stethoscope

Variations in First Apical Sound Simulating So called Presystolic Murmur of Mitral Stenosis' Phonocardio graphic Study Mariano M Alimurung Maurice B Rappa port and Howard B Sprague[3] observed by means of phono cardiography that auscultatory presystolic murmurs may at times be an auscultatory illusion owing to certain variations in the first heart sound

A presystolic murmur at the apex is generally regarded as evidence of mitral stenosis It is commonly described as having a rapidly increasing intensity with a so called cre scendo effect It is associated with auricular systole which increases velocity of blood flow through the stenosed mitral opening whereas the mid diastolic murmur generally begins with opening of the mitral valve Phonocardiography has shown that the crescendo character of the presystolic murmur is an inconstant phenomenon

The series studied consisted of eight patients all of whom were thought to have a presystolic apical murmur and yet phonocardiography failed to corroborate this auscultatory interpretation Instead certain variations of the first sound were noted which could explain the auscultatory error In most of the cases the murmur was clinically described as defi nitely crescendo The cases may be divided into three groups based on final clinical diagnoses The first group consisted of three patients who definitely had valvular disease Two had rheumatic heart disease with predominant aortic regurgitation and mitral regurgitation the other had syphilitic aortitis with aortic insufficiency In the two rheumatic cases the asso ciated apical diastolic murmur with what was believed to be a presystolic crescendo led to the additional diagnosis of mitral stenosis Without a presystolic element the diastolic murmur itself would not have suggested mitral stenosis in view of the possibility of its being an Austin Flint murmur On the other hand in the third case a suspected Austin Flint mur

(3) New Engl J Med. 241 631 636 Oct 27 1949

systole are often detected in persons who do not have heart disease

The confusion that prevails concerning the significance of loudness and character of the first heart sound is even more important Both heart sounds may be decreased in intensity if there is intervening tissue or space between the heart and the outside of the chest wall When the first heart sound is decreased and the second is not similarly affected its significance is entirely different The first heart sound is due mainly if not entirely to closure of the mitral and tricuspid valves however the abruptness or speed of ventricular systole affects the first heart sound When the contraction is hyperactive as in hyperthyroidism or anemia during effort or emotion or with certain fevers the first sound is often accentuated Valve leaflets close more abruptly and a brisk sound results There is a relationship also between the auriculoventricular interval (P R interval) and the loudness of the first sound The first sound is loudest when the P R interval is exceedingly short and generally faint when it is greater than normal From these observations it appears that when the mitral and tricuspid leaflets are wide apart or deep and low in the ventricular cavity the instant the ventricles contract the sound produced will be different (probably louder) than when they are nearer together or at a higher level If ventricles contract soon after the auricles the sound will be loud if there is delay between auricular and ventricular systole the valves will have had longer to float upward and nearly close and the first sound will be faint

Attention to intensity of the first sound as heard at the apex of the heart will often make it possible to estimate the P R interval s length and to recognize conditions in which there is a short P R interval others with a prolonged P R interval (first degree heart block) and those in which this interval is varying such as second and third degree heart block If the heart rate is regular first sound decidedly decreased and second sound normal it is fairly certain that the P R interval will be at least at the upper limit of normal or delayed systole Similarly if the rate is regular and slow and the first sound changes in intensity complete heart block with dissociation of auricles and ventricles is present It is an error to interpret a weak first sound when the second sound is nor

and the pressure therein increased Veins in the neck are of particular concern The prominent a wave in the jugular sphygmogram has been frequently referred to as has the presystolic impulse in the veins of the neck and in the liver The pronounced and chronic systolic pulsations of the deep jugular veins have also been emphasized

In a patient observed by Harry Vesell[4] (Beth Israel Hosp New York City) and found at autopsy to have tricuspid stenosis a pronounced presystolic impulse was felt over the right jugular vein just above the clavicle and over the sternocleidomastoid muscle This was of surprising force for a venous pulse It was easily timed by comparison with the systolic aortic impulse in the episternal notch palpated by the index finger of the other hand A see saw movement was conveyed to the two palpating fingers by the two vascular pulsations The strong presystolic venous impulse over the jugular vein was considered caused by the contraction of the hypertrophied right atrium this impulse was well transmitted to the neck because of the obstruction at the stenotic tricuspid orifice causing a damming back action the right atrium being unable to empty itself readily Transmission of the impulse was also aided by the increased venous distention and increased pressure in the large veins central to this area Vesell has never felt a presystolic impulse in the jugular vein in congestive heart failure without tricuspid stenosis This simple sign led to correct antemortem diagnosis in the patient observed

Xiphosternal Crunch Analysis of 106 Cases among 3 224 Army Separatees Xiphosternal crunch is a peculiar heart sound heard in the tricuspid area in normal persons Louis Schwab Gordon L Smiley and Werner P Meyn[5] emphasize the importance of recognizing the xiphosternal crunch as a common functional sound to be differentiated carefully from the sounds of pathologic significance heard in this area They found the incidence of xiphosternal crunch among 3 224 Army separatees to be 3 3 per cent Xiphosternal crunch was defined as a systolic sound of a crunching or spitting nature heard best at a point immediately to the left and above the xiphoid process in the absence of signs of organic heart disease In 58 per cent of the 106 cases in which this sound was heard

(4) Am J M d 7 497 500 O tobe 1949
(5) A I Med 31 8 234 A g t 1949

mur was not confirmed by subsequent phonocardiograms The second group comprised three patients with congenital cardio vascular anomalies coarctation of the aorta in one sub aortic stenosis in another and an undetermined anomaly as an element of Marfan s syndrome in the third In addition all were thought to have associated rheumatic mitral stenosis because of an apical diastolic murmur with the so called pre systolic crescendo In the third group of two patients mitral stenosis was diagnosed because of a presystolic murmur that was believed to be present No mid diastolic murmur was heard Phonocardiograms however disclosed no presystolic murmur Cardiac status in both cases was then declared nor mal Phonocardiograms were taken with the Sanborn Tri beam Phonocardiograph both the stethoscopic and the log arithmic microphones and the large open bell chest piece being used

The auditory illusion in these cases was due to several variant forms of the first heart sound in all of which the whole sound complex assumed a crescendo configuration The variations consisted in prolongation of the sound with its later elements of unusual intensity splitting of the sound so that the second element was more intense than the first and prolongation of the sound associated with an auricular gallop coming very close to the first sound In all variations however the first sound always started after the electrocardi ographic Q wave

Knowledge of such cardiac sound variations is important for they may produce an auditory illusion leading to serious diagnostic error in that the so called presystolic crescendo murmur at the apex is indicative of organic mitral stenosis The authors therefore emphasize caution in interpretation of this physical finding particularly in uncharacteristic cases in which the murmur may be rather short and faint and in which there is no other convincing evidence of mitral stenosis In such cases a careful phonocardiographic study is most help ful for correct clinical diagnosis

Tricuspid Stenosis Simple Diagnostic Sign. It has re cently been shown that tricuspid stenosis is not rare and that the condition can often be diagnosed clinically Venous phe nomena are usually mentioned in descriptions of tricuspid valvular disease Veins of the body are engorged and dilated

14 1 per cent were moderately loud and only 0 5 per cent were very loud

In 137 of the 500 children 157 extra cardiac sounds were detected In 100 children a physiologic third cardiac sound was best heard at the apex or slightly to the right of this point in 34 a reduplication of the second cardiac sound was found best heard in the pulmonic area or along the left sternal border in 20 a reduplication of the first cardiac sound was best recognized at the apex and in 3 a midsystolic click was heard in the midprecordium

With few exceptions those murmurs best heard in the midprecordium possessed a characteristic vibratory or buzz ing quality whereas those in the pulmonic area were basically blowing or humming Using these criteria as a guide in asso ciation with intensity pitch transmission etc identification of functional murmurs is greatly facilitated Apical location and transmission into the axilla is considered an important criterion for differentiating organic from functional murmurs However of the 182 midprecordial murmurs only 37 were audible at the apex Careful auscultation revealed that they were best heard to the right of the apex and that sounds at the apex represented diffusion of sounds which were of maxi mal intensity at another locus Thus if a murmur is audible at the apex or even to the left of it this is not a valid criterion for differentiating organic from functional murmurs A con siderable degree of association existed between occurrence of the two types of adventitious sounds Neither however was found to be correlated with degree of anemia present in the patient or with age color sex state of nutrition or tem perature

The authors concluded that the most valuable criteria for differentiating functional from organic heart murmurs in childhood are acoustic quality and point of maximal intensity Detection of innocent adventitious cardiac sounds in over one half of these children emphasizes the importance of careful cardiac auscultation

Aortic Sinus Aneurysms A Morgan Jones and F A Langley[7] (Univ of Manchester) report 2 cases of congenital and 2 of acquired aortic sinus aneurysms and compare them with 25 cases of congenital and 22 of acquired sinus aneu

(7) Brit Heart J 11 325 341 October 1949

quality of the sounds suggested crunching and in 39 per cent spitting

The sound may be caused by slight movements of the seventh costal cartilage under the cardiac thrust at its articulation with the sternum and xiphoid process Some degree of funnel chest occurred in 25 per cent of persons exhibiting the sound Possibly the abnormal sternochondral angle in this condition may favor production of the sound

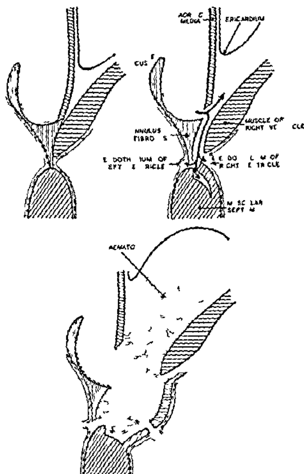
Occurrence of Innocent Adventitious Cardiac Sounds in Childhood was studied by Sidney Friedman William A Robie and T N Harris[6] (Univ of Pennsylvania) under conditions which closely simulated those in general office practice Criteria used for differentiation of functional from organic adventitious sounds were based on the results of cardiac auscultation Five hundred children aged 2 12 were given at least one special cardiac examination They were selected at random from a medical outpatient department with no reference to age, color sex or diagnosis except that those with a history or physical signs suggestive of rheumatic fever chorea congenital heart disease or hypertension were excluded Therefore all adventitious sounds noted were thought to be functional or physiologic in origin Each patient was examined in the erect and supine positions and again in recumbency following exercise consisting of 10 raise ups from the supine to the sitting position without assistance The point of maximal intensity transmission pitch intensity and quality of adventitious sounds were recorded Pulse rate was counted before exercise and before cardiac rhythm was noted

Of the 500 children examined 234 (46 8 per cent) had systolic murmurs over some area of the precordium All the murmurs were considered nonpathologic Of these 182 were of the greatest intensity in the midprecordium i e in the third fourth or fifth interspaces to the left of the sternum but definitely to the right of the apex In 91 children murmurs were loudest in the pulmonic area Thirty nine children had two separate murmurs each with its own point of maximal intensity and characteristic quality Ten children were found to have murmurs loudest at the apex and 1 loudest at the aortic area Thus in 234 children a total of 273 murmurs were detected Of the 273 murmurs 85 4 per cent were barely audible

(6) Ped i cs 4 782 789 December 1949

rysms collected from the literature Acquired aneurysms may arise from any of the aortic sinuses Because of their large size they tend to extend upward often becoming extracardiac and rupturing outside the heart Cardioaortic fistulas were present in only six cases They encroach on intracardiac structures less often than congenital aneurysms Congenital cardiac defects were present in only two cases but acquired heart disease was invariably present usually syphilis or bacterial endocarditis In one of the present cases there was a dissecting aneurysm arising in the right coronary sinus at the junction of the aortic media with the annulus fibrosus (Figs 86 90) It is probable that the dissection arose as a result of active aortitis possibly rheumatic in origin

Congenital sinus aneurysms are confined to the right coronary sinus and the adjacent two thirds of the noncoronary sinus They are always small but because of their thin walls commonly rupture to form cardioaortic fistulas usually communicating between the right coronary sinus and the right ventricle or between the noncoronary sinus and the right atrium They remain entirely intracardiac and do not affect extracardiac structures nor rupture outside the heart They frequently cause disturbance of intracardiac structures especially the pulmonary valve which is often interfered with by right coronary sinus aneurysm and the tricuspid valve which may be encroached on by aneurysm arising from either sinus Congenital sinus aneurysms are nearly always associated with other developmental faults usually anomalies of the aortic cusps or bulbar ventricular septal defects Apart from bacterial endocarditis acquired heart disease occurred in only one case These aneurysms are believed to arise from defective development of the distal bulbar septum The patients are usually male In eight cases x ray studies disclosed no evidence of localized aneurysmal swelling Electrocardiographic findings were so inconstant that they gave little assistance in diagnosis The cause of death in 15 of 25 cases from the literature was heart failure which in 12 could be attributed to rupture in 2 to congenital cardioaortic fistulas and in 1 to rheumatic heart disease associated with an unruptured aneurysm Bacterial endocarditis led to death in six cases and intercurrent disease was the immediate cause of death in four Although it is difficult to diagnose an unruptured aortic sinus



F g 88 (top left) —\ m l tru ture f o t r t n sect n thr gh r ght co na y nus D tribut n f l t c t u hown by ter upt d l ne Structu s are named n F gur 89

F g 89 (top ght) —Mode of d sect n An ulus fib o ha been sepa ted from terminat n of ao t m d a Sub equ nt d t ns of d s ect on a e nd cated by arr ws

F g 90 (bottom) —An u y m. By comp son w th F g re 89 the w y in which aneury m has form d an be seen

(Courtesy of Jon A M nd La gl y F A Br t H art J 11 325 341 October 1949)

arctation of the aorta in whom surgery had not been under taken is pre ented by Bertrand G Wells Maurice B Rappaport and Howard B Sprague[9] (Boston) Coarctation was considered to be uncomplicated in all but one patient in whom the additional diagnosis of aortic regurgitation was made clinically Opinions differ as to which murmurs are characteristic in uncomplicated coarctation of the aorta and which are due to concomitant defects

A systolic murmur was pre ent over the dorsal spine in all 15 patients and over the precordium in all but 1 A diastolic murmur was pre ent in six patients over the dorsal spine and in five over the precordium Both systolic and diastolic murmurs were occasionally of greater intensity over the dorsal spine than over the precordium Such a di tribution of intensity i never pre ent in murmurs of isolated aortic valve deformity or patent ductu arteriosus and in none of the 15 patients were murmurs louder over collateral vessels than over the dorsal spine It i therefore probable that both systolic and dia tolic murmurs are frequently present in uncomplicated coarctation of the aorta

Phonocardiographic tracings revealed the following facts Significant diastolic vibrations were present in tracing from the dorsal spine in every patient although in only six was a dia tolic murmur heard Diastolic vibrations were characteristically of decre cendo configuration being a continuation from the systolic murmur Diastolic vibrations from the precordium were recorded in 10 patients although a diastolic murmur was heard in only 5 of the e However the vibrations were usually of different configuration from those recorded from the dorsal spine and were therefore caused by a different mechanism in most instances the configuration of these vibrations resembled that in aortic insufficiency

The authors believe that systolic and diastolic vibrations from the dor al pine are found on phonocardiography even more characteristically than they are heard on auscultation Reason that dia tolic vibrations may not be audible as a diastolic murmur are intensity of a loud systolic murmur may be uch a to fatigue the human hearing mechani m which ould mask the murmur in early diastole frequent absence of the econd heart sound on auscultation over the back may

9 Am. Heart J 38 69-79 J ly 1949

aneurysm it is one of the silent congenital lesions to be suspected when bacterial endocarditis develops in a heart apparently previously healthy

CONGENITAL HEART DISEASE

The recognition of the various types of congenital anomaly of the heart is no longer a matter of academic interest but involves the practical decision of operability The articles presented here are valuable in this respect In view of the increasing interest in the surgical treatment of the cyanotic types of congenital cardiac disease it is important to realize that arteriovenous communications in the lung may produce a clinical state characterized by cyanosis polycythemia and clubbing of fingers Diagnosis and treatment of this condition are considered in the last abstract of this chapter —Ed

Circulation Times in Congenital Heart Disease K D Allanby[8] (Guy s Hosp London) reports results of estimating arm tongue and arm lung times in 36 patients suspected of having congenital heart disease Agents used were 20 per cent sodium dehydrocholate and 50 per cent saccharin for arm tongue time and 5 per cent paraldehyde for arm lung time There were no fatalities and no evidence of venous thrombosis or other complication except that about half the subjects complained of pain in the arm after paraldehyde and two became nauseated after decholin*

Results showed that measurement of arm tongue and arm lung times together is a reliable simple and safe method to be used for diagnosis of a right to left shunt It is most important that both times be estimated together as the only satisfactory evidence of a shunt is that they agree within two seconds of each other This alone can indicate that substances introduced into the right side of the heart reach a point on the great and lesser circuits simultaneously and there must be a communication between the two before the lung capillaries are reached Further the blood must be passing from right to left Failure was encountered in only three cases and in these it was attributed to use of too little saccharin Five patients had normal arm tongue times in each the arm lung time equaled this demonstrating the possibility of error if arm tongue time is taken alone as a guide to the presence or absence of a shunt

Sounds and Murmurs in Coarctation of Aorta Study by Auscultation and Phonocardiography on 15 patients with co

(8) Brit Heart J 11 165 169 Apr 1 1949

shadow made by the ascending aorta and evidence of anterior displacement of esophagus and trachea in the left anterior oblique view Since surgery apparently gives permanent relief from symptoms clinical diagnosis of a double aortic arch is important

Analysis of 49 cases proved at autopsy or operation to have a double aortic arch with or without obliteration of part of the left arch revealed a striking correlation between occurrence of severe symptoms and duration of life All but 2 of the 19 infants had symptoms referable to the double aortic arch Fourteen of the 17 infants with symptoms died as a direct result of the malformation surgery was successful in 3 of 5 infants The high mortality in infants was in striking *contrast to that in older patients of 23 patients over age 2* all but 6 lived to be 39 or older and only 3 had symptoms referable to the double aortic arch This analysis indicates that if a double aortic arch causes symptoms of constriction the symptoms will develop during the first two years of life Surgery is indicated only in patients who have such symptoms It cannot be stressed too strongly that incidental finding of a double aortic arch is not an indication for surgical division of the arch Operative mortality is high two of seven patients who underwent surgery died

A double aortic arch in which both components are patent throughout *is more likely to produce symptoms* than a double aortic arch in which one component is partially obliterated The process of obliteration does not appear to cause symptoms If obliteration occurs only the left component has been involved in all cases reported It is unusual for a double aortic arch to be associated with malformation of the heart though its association with other vascular abnormalities is less rare

Congenital Aortic Septal Defect. A defect in the wall of the ascending aorta leading to free communication with the adjacent pulmonary artery is a rare congenital abnormality The opening in the anterior wall of the aorta is just above the semilunar cusps and leads directly into the pulmonary artery J H Dadds and Clifford Holye[2] (London) report an example of this anomaly of value chiefly because there were no other congenital defects

Boy 14 was hospitalized for increasing dyspnea on exertion and

(2) Brit. Heart J 11 390 397 October 1949

obscure the fact that the murmur extends into early diastole

Synchronous records of radial and femoral pulses can be recorded satisfactorily and the authors believe that demonstration of abnormal asynchronism constitutes a valuable test in diagnosis of coarctation of the aorta and should be more widely used

Double Aortic Arch Report of Two Cases and Review of Literature is presented by Herbert E Griswold Jr and Maurice D Young[1] (Johns Hopkins Univ) A double aortic arch results from persistence of both fourth branchial arterial arches the arches fuse with the dorsal aortas to form the descending aorta resulting in a vascular ring Usually a large right aortic arch passes to the right of the esophagus and trachea in a posterior direction turns to the left passing behind the esophagus and trachea and connects with a small left aortic arch The small left aortic arch passes laterally to the left in front of the trachea and then turns posteriorly to join the right aortic arch which continues downward as the left descending aorta Usually the right common carotid artery and then the right subclavian artery arise independently from the right aortic arch the left common carotid artery and the left subclavian artery arise from the left aortic arch

The clinical picture of stridor and dysphagia may be present during the first few months of life because of constriction of the esophagus and trachea by the double aortic arch Criteria for diagnosis of a double aortic arch include susceptibility to bronchopneumonia stridulous breathing chronic cough head retraction malnutrition and increased respiratory distress during feeding Clinical signs are dulness to the right of the sternum visible systolic pulsation in the right supraclavicular fossa displacement of trachea to the left tracheal tug obstruction to free passage of a stomach tube at the level of the third dorsal vertebra with pulsation transmitted along the tube and maximal intensity of the aortic second sound in the region of the head of the right clavicle

Roentgenographic criteria include shadow of the aortic knob lying to the right and displacing the esophagus and trachea to the left in the anteroposterior position the aorta lying behind the trachea and esophagus and displacing them anteriorly in the right anterior oblique position a wide

(1) Pediatrics 4 751 768 December 1949

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(2) B t H t J 11 390 397 O tob 1949

for palpitation He had had difficulty in breathing since infancy and activities had been severely curtailed He was a pale stunted youth with a kyphotic chest the anterior wall of which bulged forward prominently on the left side Cardiac pulsation was diffuse and thrusting with the impulse maximal in the seventh space 16 cm left of the midline The beat was regular A diastolic thrill was palpable just inside the cardiac impulse and also left of the sternum at the base Systolic and diastolic murmurs were heard all over the pre cordia the latter louder in the pulmonary area and just internal to the impulse The systolic element loudest in the aortic area was well conducted to the root of the neck Both heart sounds were audi ble in all areas and the pulmonary second sound was accentuated Blood pressure was 130/40 and pulse collapsing Neither cyanosis nor clubbing were present nor had he any congestive failure

Radioscopy showed a huge aneurysmal shadow comprising the pulmonary artery and aorta astride the greatly enlarged heart The aortic component was normally located but very pulsatile No sep arate aortic knuckle could be seen In oblique views the ascending aorta was prominent and a barium swallow showed a combined aortopulmonary impression Both ventricles were large the right larger than the left There was a pronounced hilar dance

In the next few months the patient had recurrent fainting spells and increasing loss of breath and died in congestive heart failure one year after study At autopsy the heart greatly enlarged was found to be surmounted by a large aneurysmal sac comprising the main pulmonary artery and the contiguous aorta Both ventricles were hypertrophied and dilated particularly the right one Auricles were not enlarged Septa were normal The aneurysmal sac showed a wide communication between the hugely dilated pulmonary artery and the base of the aorta just above the valves The defect measured 6 × 5 cm The aorta itself was hypoplastic Other organs were normal aside from congestion

Though survival is variable in congenital aortic septal de fects the physical limitations the defects impose appear to be almost uniform Symptoms of cardiac insufficiency from early infancy are always recorded Most patients died in congestive heart failure Cardiac murmurs reported in 11 cases vary greatly Basically the signs are similar to those of any other free leakage from the aorta above the cusps as with a patent ductus The heart is always enlarged especially the right side Site of the defect is remarkably constant and the lower border is formed by a smooth ridge of tissue separating the aortic and pulmonary sinuses The defect is usually small and the fine smooth edges are characteristic and distinguish the con genital from the commoner acquired communication between aorta and pulmonary artery Other congenital cardiovascular

defects are usually absent Clinical diagnosis of congenital patency of the aortic septum is difficult In none of the recorded cases was diagnosis made in life In this case the authors believed they were dealing with a complicated defect including a patent ductus arteriosus and probably an atrial septal defect Diagnosis depends primarily on signs of a free leak from the aorta in the presence of a dilated pulmonary arterial tree and enlargement of both ventricles Such a combination is rare enough if patent ductus either alone or with an atrial septal defect is excepted When patent ductus is the sole abnormality enlargement of the heart and of the pulmonary artery and its branches is rarely as striking as that found with large aortic septal defects If the aortic septal defect is small the difference from a patent ductus is less obvious Perhaps in the future retrograde angiocardiography may resolve the difficulty It is said to outline a patent ductus clearly and would almost certainly show the site and size of an aortic septal defect

Congenital Tricuspid Atresia Classification, by *Jesse E Edwards and Howard B Burchell*[3] *is based on study of 42* cases reported in the literature and 3 cases observed personally The circulatory defect in congenital tricuspid atresia may be described simply as a functional two chambered heart Common to all cases are atresia of the tricuspid orifice patency of the atrial septum and a large mitral orifice leading into a large ventricular chamber Atresia of the tricuspid orifice is represented by the absence of a right atrioventricular orifice Patency of the atrial septum is in most cases represented by a retention of the fetal type foramen ovale

Relation of the great vessels to each other and to the ventricular part of the heart varies among cases of tricuspid atresia The varieties of interarterial and arterioventricular relations constitute four groups which form the basis for the anatomic classification of congenital tricuspid atresia presented (1) no transposition of the great vessels and (*a*) pulmonary atresia closed ventricular septum or (*b*) subpulmonary stenosis (2) transposition of the great vessels and (*a*) pulmonary or subpulmonary stenosis or (*b*) no pulmonary or subpulmonary stenosis

In type 1a the left ventricle has a large capacity and its

(3) M Cl n N th Am 33 1177 1196 J ly 1949

wall is thick The ventricular septum is completely formed The right ventricle is minute lies virtually hidden in the right upper wall of the large left ventricle and plays no role in circulation It is merely an isolated endocardial lined chamber since both the tricuspid and the pulmonary valve orifices are atretic The pulmonary atresia usually occurs at valve level the pulmonary trunk above valve level being hypoplastic but patent Death during infancy is the rule in patients with this type of tricuspid atresia

Type 1*b* is the most common of tricuspid atresias The great vessels are *correctly interrelated* The pulmonary trunk is somewhat narrower than normal but usually of adequate caliber to be able to carry a sufficient amount of blood to the lungs were there no subpulmonary stenosis A large ventricular chamber into which blood flows through the mitral orifice freely communicates with the aorta and communicates by means of a narrow tract with a smaller narrow ventricular chamber *The upper extremity of the small ventricular chamber* communicates with the pulmonary orifice The tract connecting the two ventricular chambers is narrow and constitutes the major barrier to blood flow from the larger ventricular chamber to the lungs Mean age at death of 22 patients with this type of tricuspid atresia was 7 months

As in all types of tricuspid atresia type 2*a* displays a large mitral orifice which leads into a large ventricular chamber Transposition of the great vessels is present There is also a diminutive ventricular chamber lying along the right side of the larger chamber which appears as a diverticulum While stenosis may exist at valve level and in the pulmonary trunk it is usually subpulmonic

In type 2*b* the malformation is identical with type 2*a* in all respects except for the state of the pulmonary circulation In type 2*b* the pulmonary trunk arises posterior to the aorta as in type 2*a* but there is no pulmonary or subpulmonary stenosis Judging from the reports on tricuspid atresia it is apparent that among patients with transposition of the great vessels those with subpulmonary or pulmonary stenosis have a much better chance of survival than those in whom no barrier to pulmonary blood flow exists

It has been suggested that transposition of the great vessels would favor longevity in cases of tricuspid atresia How

ever presence or absence of transposition per se will not determine degree of anatomic obstruction to pulmonary flow Survival to adulthood seems determined in part by chance but probably also by a balanced systemic and pulmonary blood flow In tricuspid atresia of type 2*b* and perhaps in type 1*a* wherein there is no barrier to pulmonary flow it is doubtful that benefit would be derived from an anastomotic operation such as the Blalock Taussig There is in contrast to the situation in the other two types of tricuspid atresia in which there is a barrier to pulmonary flow and in which an anastomotic operation is of benefit

Occurrence of Chronic Cyanosis in Cases of Atrial Septal Defect Atrial septal defect has been classified as a late cyanotic lesion one associated with cyanose tardive terminal cyanosis due to a reversal of the direction of the intracardiac shunt which occurs with cardiac failure increasing pressure in the right auricle It has also been stated that in atrial septal defect there is never the intense cyanosis and concomitant clubbing which are so characteristic of a venous arterial shunt Arthur Selzer and Alvin E Lewis[4] (Stanford Univ) observed a patient 35 with chronic cyanosis polycythemia and clubbing of digits who at autopsy was found to have an uncomplicated atrial septal defect They therefore reviewed autopsy reports in cases of atrial septal defect collected from the literature in which chronic cyanosis was observed

Of 180 cases of proved atrial septal defect with or without concomitant mitral stenosis 11 were thought to represent atrial septal defects with chronic cyanosis Cyanosis had been present since birth in two patients and in most of the others it appeared in the second decade Cyanosis was described in most cases as moderate in some as severe Clubbing was present in all except one Polycythemia was reported in seven Histologic findings in these cases did not differ from those in other noncyanotic cases Large defects involving most of the atrial septum were common among cyanotic patients but there was no apparent relation between size of the defect and presence of cyanosis Complicating mitral stenosis apparently rheumatic in origin was recorded in three cases

It is thus apparent that cyanosis not related to cardiac fail

(4) Am J M S 218 516-524 N mbe 1949

ure may occur in cases of atrial septal defect with or without complicating mitral stenosis Degree of cyanosis and of accompanying polycythemia and clubbing and age of their onset places some of these cases definitely in the cyanotic group of congenital heart disease though they constitute only a small fraction of the total number That atrial septal defect may take the form of morbus caeruleus introduces a new problem in differential diagnosis of congenital heart disease With cyanosis moderate in degree and appearing in late childhood differential diagnosis between the Eisenmenger complex and atrial septal defects may be impossible by ordinary means and may have to rest entirely on results of venous catheterization of the heart

In addition to the diagnostic difficulty this problem raises the question whether cyanosis associated with atrial septal defect is due to the congenital defect itself or to complicating and secondary factors With the clinical and pathologic evidence pointing to a large volume of blood being shunted from the left to the right auricle the most likely cause of cyanosis appears to be a free mixing of blood in large septal defects and/or anatomic conditions permitting a stream of venous blood from the great veins to enter the left auricle directly

Arteriovenous Aneurysm of Lung To stress the importance of earlier recognition of a treatable condition Charles Baker and J R Trounce[5] (Guy s Hosp London) report two cases and review present knowledge of this disease Case 1 follows

Man 27 was referred for supposed cyanotic congenital heart disease to see if he was suitable for a Blalock Taussig operation Cyanosis which was gradually and steadily progressive was noticed at age 4 and a year later a diagnosis of congenital heart disease was made

Examination revealed a spare well built man with gross cyanosis and marked clubbing of fingers and toes He was breathless on slight exertion but there was no orthopnea Neck veins were not distended liver was just palpable but not tender Lung bases did not sound wet but there was slight pitting edema of the ankles. Pulse was regular Heart showed no clinical enlargement and no murmur Pulsation in the second left intercostal space was the only finding of note Screening showed a heart slightly enlarged (13/25 cm) with the pulmonary conus prominent and an enlarged right ventricle In the

(5) Brit Heart J 11 109 118 Ap 1 1949

right lower lung field there was a circumscribed shadow with a well defined margin calcified in its lower part This was connected to the right hilus by a vascular shadow and there was pulsation from hilus to tumor An electrocardiogram showed marked right axis deviation with broad and prominent P waves in leads I and II and an inverted T in lead III

After the shadow in the lung had been seen the two important points needed to clinch the diagnosis of arteriovenous aneurysm were looked for and found On listening at the right base posteriorly there was a well marked localized systolic murmur but no diastolic element Angiomas were found on the inner side of the lips and on the buttocks and it was clear that a seborrheic disfigurement and the deep cyanosis had masked small angiomas on the face Blood picture showed severe polycythemia

Diagnosis of arteriovenous aneurysm of the lung was made and operation performed During operation the right middle lobe bronchus was wounded and it was necessary to remove both the right lower and middle lobes This was difficult because of multiple vascular adhesions to the chest wall and diaphragm and there was considerable blood loss Although cyanosis disappeared the patient s condition remained poor after surgery X ray revealed complete collapse of the right upper lobe and de pite bronchoscopy he died some 30 hours after operation

Examination of the surgical specimen revealed that the pulmonary vein leaving the lower lobe was grossly dilated and communicated with a large thin walled loculated system of spaces Cut surface of the lower lobe howed a multilocular hemangioma A branch of the pulmonary artery communicated directly with this cavernous space without capillary intervention Sections showed typical cavernous hemangioma

Cyanosis from childhood or early adult life with clubbing and polycythemia are the most important features of arteriovenous aneurysm of the lung Physical signs in the heart are uncommon but a murmur may be heard in the chest corresponding to the invariable finding of an opacity in lung x rays Associated vascular lesions in skin mucous membranes and lips are common Cyanosis is slowly progressive and is followed by dyspnea restricted activity and eventually incapacity Hazards to life are from anoxemia polycythemia and hemorrhage from the aneurysm rather than from heart failure The commonest misdiagnosis in early life is congenital heart disease but the condition may also be mistaken for polycythemia rubra vera if cyanosis first develops in adult life or pulmonary tuberculosis when hemoptysis occurs with the undiagnosed x ray opacity

Arteriovenous aneurysm of the lung is successfully treated

by removal of the aneurysm by lobectomy or by pneumonectomy Surgery is a reasonable risk and indicated in patients with lesions large enough to cause cyanosis

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RHEUMATIC HEART DISEASE AND BACTERIAL ENDOCARDITIS

Induction of Cardiac Lesions, Closely Resembling Those of Rheumatic Fever, in Rabbits Following Repeated Skin Infections with Group A Streptococci Experiments have shown that focal infections of rabbits with Streptococcus viridans group A or C resulted in development of clearcut cutaneous and general hyperreactivity to the homologous infecting strain which was enhanced by frequent minute intracutaneous inoculations These observations led George E Murphy and Homer F Swift[6] (Rockefeller Inst) to become interested in the similarity of these phenomena to rheumatic fever in human beings and to investigate whether such animals had cardiac lesions resembling those of rheumatic heart disease Because of the difficulty of repeatedly infecting rabbits' throats and sinuses it was decided to inoculate the skin every month or twice a month with group A streptococci of different serologic types different types having been found to produce greater hypersensitivity than repeated infections with one type of organism

Animals were given 2 10 injections of streptococci of different serologic types during 3 20 months An elevated erythrocyte sedimentation rate leukocytosis anorexia weight loss postexertional dyspnea occasional transient pulmonary rales tachycardia and irregularity of cardiac rhythm developed in many of them

Microscopic examinations of the hearts of rabbits which died of infection or were killed while ill revealed focal alterations in connective tissue framework in blood vessel adventitia valves endocardium epicardium and myocardium Collagenous fibers were swollen eosinophilic and sometimes poorly stained Among such cells were found nodular collections of large irregularly shaped cells of unusual staining

(6) J Exper Med 89 687 698 Jun 1949

properties in most instances these granulomas were associated with capillaries Interstitial valvulitis most marked in the middle of the cusp were observed on mitral and aortic valve leaflets and also on the right auriculoventricular valve The coronary arterial system was likewise involved and microscopic changes resembling those seen in patients with rheumatic fever were observed Neither bacteria nor any structures resembling inclusion bodies were seen

Since the cardiac lesions found in these animals were not found in control animals it was concluded they were due to successive cutaneous infections with group A streptococci of different types The striking histopathologic resemblance of these lesions to human rheumatic fever is of great interest

Subacute Bacterial Endocarditis Diagnosis and Present Day Treatment In the experience of Leo Loewe[7] (Long Island College of Medicine) positive blood cultures can be obtained in 85 95 per cent of patients with subacute bacterial endocarditis In the absence of positive blood cultures clinical diagnosis is generally accepted in patients with rheumatic or congenital heart disease an insidious illness with weakness and low grade fever and cutaneous or visceral embolization and splenomegaly When diagnosis rests between subacute bacterial endocarditis and rheumatic fever trial administration of penicillin should be made

In approximately 90 per cent of cases the infecting agent is streptococcus of the viridans or nonhemolytic type Cultures on suitable mediums must be seeded at the bedside and incubated promptly Pour plates should be made as they often facilitate interpretation of questionable broth cultures Inoculum of blood must be adequate If the patient is under penicillin treatment cultures should contain penicillinase to counteract penicillin All blood cultures should be incubated for three weeks before they are declared negative

In vitro sensitivity of the organism must be determined in every case Organisms inhibited by less than 0 1-0 5 units of penicillin/ml of test broth are considered sensitive to daily dosages of 2 000 000 units of penicillin Patients with organisms requiring 10 30 units/ml or even more of test broth may be given prodigious daily dosages (10-40 million units) of penicillin with or without enhancing agents such as sodium

( ) Am P ct 1 349 361 Ap 1 1950

para aminohippurate or preferably carinamide Carinamide 3 4 Gm every four hours is given orally day and night except in patients with impairment of renal function No serious side effects have been encountered

Intensive penicillin therapy is continued for four to five weeks If relapse takes place and this is usually evident within two weeks larger doses must be given and continued for a longer time at least eight weeks Continued positive blood cultures for more than a few days after starting treatment are considered unequivocal evidence of inadequate dosage In Loewe s series of 124 unselected consecutive patients with subacute bacterial endocarditis due to known organisms recovery took place in 104 Total penicillin dosage ranged from 1 400 000 to 927 000 000 Oxford units If despite acceptable penicillin blood levels the clinical picture suggests that infection is not being satisfactorily controlled streptomycin aureomycin or chloramphenicol may be given in addition If blood cultures are negative treatment must be determined clinically

To prevent subacute bacterial endocarditis foci of infection should be eradicated and antibiotics used when respiratory dental or other infections occur in patients with valvular heart disease In addition because there is a tendency to recurrence patients who have recovered from subacute bacterial endocarditis may be vaccinated Loewe vaccinated 56 recovered patients with a polyvalent vaccine composed of five strains isolated from the blood stream of patients during the active phases of the disease Results to date have been encouraging

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HYPERTENSION

In examining a patient with hypertension the physician should seek first for those causes which are curable such as tumor of the adrenal medulla or coarctation of the aorta Most patients with hypertension fall into the essential group the etiology of which remains uncertain In properly selected cases sympathectomy has a beneficial effect but is rarely curative The same may be said for psychotherapy Drastic restriction of sodium in the diet is beneficial in many younger patients but is usually ineffective in the older group Recent experimental studies indicate that there may be other dietary factors such as the intake of protein or of total calories Reports on the veratrum alkaloids are encouraging particularly those regarding protoveratrine Further investigation of these compounds is merited.—Ed.

Certain Pressor Depressor Tests in Essential Hypertension Comparison and Comment A number of procedures have been used to test maximal and minimal variations in patients with high blood pressure The cold test breathholding test posture test and response to mental stress are pressor tests Sodium amytal® or pentothal® sedative tests spinal block intravenous administration of tetraethylammonium and hyperventilation with carotid sinus pressure are some of the depressor tests

To determine how well these procedures reveal the range of variation and the maximal and minimal levels which occur spontaneously Teodoro Postelli (School of Medicine Bologna Italy) and Robert Sterling Palmer[8] (Massachusetts Gen l Hosp) compared certain of these tests with observed spontaneous variations in 123 unselected patients with hypertension A combined posture and cold test the breathholding hyperventilation carotid sinus pressure test sodium amytal® sedative and mental stress tests were studied

Results of these procedures were simply to emphasize what is already known namely that blood pressure in essential hypertension is variable In the authors opinion variability of blood pressure as revealed by these tests does not classify hypertension into different grades and the variabilities are doubtful guides to prognosis and selection of patients for medical or surgical treatment Of these so called tests the simplest and least time consuming is the breathholding hyperventilation carotid sinus pressure test The mental stress test is useful in demonstrating the pressor factor to the patient and thereby encouraging acceptance of psychotherapy

In contrast to these maneuvers which demonstrate vascular *hyperreactivity in essential hypertension there remain two* tests worthy of the name because they are seemingly specific *The first* is the histamine test for pheochromocytoma of the adrenal gland It is dangerous but may be indicated when blood pressure is normal—though not if the history includes *characteristic attacks of the pheochromocytoma syndrome* and not if a typical attack occurs under observation The second test safer because it is a depressor test is use of benzodioxane It *seemingly* is *specific for pheochromocytoma* when blood pressure is elevated between attacks The physi

(8) Am. P ct. 4 9 13 Septembe 1949

cian should be alert to this possibility and the test should be used even though many negative results may be anticipated

Follow up Study of 243 Cases of Eclampsia for Average of 12 Years is presented by Charles I Bryans Jr, and Richard Torpin[9] (Univ of Georgia) Subsequent pregnancies (565) occurred in 188 women Of these 22 9 per cent resulted in either stillbirth or abortion (almost twice that expected in general) At least 203 pregnancies (36 1 per cent) were complicated by toxemia and 56 4 per cent of the 188 women had at least one toxemic pregnancy (four to six times the general rate of occurrence) Eclampsia recurred 27 times One woman had two subsequent attacks Incidence of repeated eclampsia was 4 8 per cent (7 32 times greater than the usual rate reported by various authorities) Previous to the original attack of eclampsia there had been 287 pregnancies in 82 women Of these 7 7 per cent were toxemic—approximately the usual incidence of toxemia

During the follow up period 27 women died 4 of eclampsia 5 of some manifestation of cardiovascular disease 4 of chronic glomerulonephritis and the others of unrelated causes Blood pressure of 47 women (21 4 per cent) was 140 or more systolic or 90 or more diastolic Incidence of hypertension in white women was 17 7 per cent and in Negroes 26 per cent Mean age of the white women was 43 7 years and of the Negroes 35 2 years For women of this age group incidence of hypertension was not significantly high However among the younger women hypertension was found more often than would be generally expected Elevated blood pressure was present in 8 9 per cent of women aged 20 29 Incidence of abortion or stillbirth and of toxemia was lower in the subsequent pregnancies of the hypertensive women than in those with normal blood pressure This was also true in the pregnancies preceding the original attack of eclampsia

The authors conclude that eclampsia is a specific disease of pregnant women and not a manifestation of chronic nephritis or of hypertensive cardiovascular disease although either of these conditions may precede the attack of eclampsia and possibly make the patient more susceptible to toxemia Neither does eclampsia or nonconvulsive toxemia cause chronic nephritis or hypertensive cardiovascular disease Pa

(9) Am J Ob t & Gyn c 58 1054 1065 December 1949

tients who have once had eclampsia or pre eclampsia are more likely to have subsequent toxemia and a high incidence of stillbirths and abortions because the same etiologic factors environment diet etc are likely to remain more or less constant and to provoke the same results in subsequent pregnancies

Prognosis in Arterial Hypertension Comparison between 251 Patients after Sympathectomy and Selected Series of 435 Nonoperated Patients was made by Sven Hammarstrom (Stockholm) and Poul Bechgaard[1] (Aarhus Denmark) The patients who were operated on were followed two to eight years and included all hypertensives operated on at the Neurosurgical Clinic of Serafimer Hospital Stockholm from February 1940 to August 1946 except three who have not been traced Five patients died as a result of the operation Since 1943 there has been no operative mortality in a consecutive series of 250 hypertensives Bilateral lumbodorsal ganglionectomy and splanchnicectomy from the ninth thoracic to the first lumbar level according to Smithwick s method was done on 148 patients of these 24 later died Another 64 were operated on bilaterally according to Peet s method of these 13 later died In 31 patients operation was done on one side only 18 of these later died

Patients not treated surgically were selected according to the same rules as the surgical subjects and followed for 2 10 years

Patients were divided into four groups men and women were treated separately Group I was not included in this study as it contained patients with uncomplicated hypertensive disease and no marked subjective symptoms Patients with such benign hypertension were not selected for sympathectomy Group II included those with pronounced subjective symptoms but no signs of myocardial damage Retinal changes in this group were classified as group 1 or 2 according to Keith and Wagener Group III included patients with the same eyeground changes or in addition retinal hemorrhages with or without signs of thrombosis of retinal vessels These patients further showed one or more of the following signs of cardiovascular damage negative T_1 in the electrocardiogram heart volume above the predicted normal resid

(1) Am. J M d. 8 53 56 Jan ry 1950

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numbness of tongue lips and extremities carpopedal spasm and nausea Massage over the adrenal areas failed to produce any at tacks Hyperventilation easily produced headaches carpopedal spasm and a rise *in blood pressure from 184/122 to 244/150* Intravenous urograms failed to reveal any deformity or tumor Perirenal aero grams also failed to outline an adrenal mass Exploration through bilateral lumbar incisions revealed a normal right adrenal gland and a well encapsulated tumor the size of a large egg in the left *adrenal area This was completely excised Recovery was complete* and 18 months later the patient was entirely normal

Clinical attacks are the most impressive feature of the syndrome produced by pheochromocytoma Attacks last a few minutes to a few hours occasionally two or three days At on set of an attack palpitation is common with headaches and pain in the precordium or epigastrium and nausea and vomit ing Anginoid pains epigastric pain roaring in the head occipital headache heat in the face and sneezing are other symptoms Blood pressure may be normal but is usually ele vated between attacks Hyperglycemia and glycosuria occur in about one fourth of patients Thyroid enlargement and ele vation of basal metabolic rate are not uncommon An un usually high incidence of generalized neurofibromatosis has been reported in pheochromocytoma

Pheochromocytomas originate from the chromaffin tissue system Chromaffin tissue is widely scattered Tumors have *been reported to arise from the intrathoracic sympathetic* chain from below the bifurcation of the aorta from the coc cygeal body from the carotid body and in the wall of the intestine but none of these has produced the cardiovascular picture *Only those in adrenal glands or in the retroperitoneal* tissue between the kidneys have shown associated hyperten sion Tumors of all sizes have been reported varying from a few centimeters to melon sized masses They are sometimes malignant

Paroxysmal hypertension has been reported with adrenal ganglioneuromas with neuroblastomas and with adrenal cortical tumors In patients with pheochromocytomas attacks can sometimes be induced by hyperventilation by massage over the adrenal area or by changes in posture Histamine acid phosphate 0 1 cc of 1 1 000 given rapidly intravenously produces little effect in normal persons but in those with a pheochromocytoma may cause a severe paroxysm of hyper

ual damage after cerebral insult and constant albuminuria Group IV included all hypertensives with definite retinal exudates and/or papillary protrusion since life expectancy was found to be about the same whether papillary protrusion was or was not present

Prognosis was found to be consistently better in the patients operated on than in the controls In patients with retinal exudates (group IV) this difference was statistically significant in both sexes In groups II and III mortality rate was more than twice as high in men as in women In men with signs of cardiovascular damage (group III) prognosis was significantly better in those operated on than in the controls The lower mortality rate in group III women who were operated on compared with controls in this group was less significant but was still 60 per cent In group II patients life expectancy is favorable and a longer follow up is needed to decide if neurosurgical treatment significantly improved prognosis

Sustained Hypertension Due to Pheochromocytoma Report of Case Cured by Removal of Tumor is presented by Hugh P Smith Jr R Bruce Logue and Donald E Beard[2] (Emory Univ)

Man 23 was hospitalized complaining of headaches and weakness of the legs of approximately 18 months duration Symptoms had begun shortly after he had been rejected by the Army because of hypertension Headaches usually occurred when he wakened and were less severe during the day They recurred for two or three days and then did not appear for several more days Hot weather and physical exertion seemed to initiate them The patient also noted one to three day episodes of weakness in the legs

On admission blood pressure was 240/124 Examination revealed no abnormality except extreme constriction of the retinal arterioles without hemorrhages or exudates a slightly enlarged heart with a grade I systolic murmur at the apex and frequent extrasystoles White cell count was 17 800 In 14 urine specimens specific gravity varied from 1 002 to 1 012 Urinary output averaged 3 000 4 000 cc. daily A trace of sugar was noted in the urine on one occasion An electrocardiogram showed left ventricular hypertrophy

Amytal* sedation lowered blood pressure from 190/112 to 154/94 Cold pressor test showed practically no rise Tetraethyl ammonium chloride caused no significant change in blood pressure. When 0 037 mg histamine base was given intravenously blood pressure fell immediately from 205/130 to 136/70 then rose precipitously to 260/146 the reaction was severe—flushing hyperventilation

(2) C culat on 1 454 460 M b 1950

impressions of the patient s sensorium and ophthalmoscopic observations of eyegrounds suggest that these areas receive adequate circulation during hypotension

Wilkins observed the effect of V viride in two small groups of patients Vertavis* was administered to 34 patients for 1 13 months Eleven per cent had a lowering of 50 mm or more and 70 per cent a lowering of 20 mm or more in average systolic pressure 14 per cent had a decrease of 30 mm or more and 41 per cent a decrease of 20 mm or more in average diastolic pressure Similarly in 20 patients to whom an experimental drug veriloid was given for 6 20 weeks aver age systolic pressure was reduced 50 mm or more in 50 per cent and 20 mm or more in 70 per cent and diastolic pressure 30 mm or more in 50 per cent and 20 mm or more in 70 per cent In both groups arterial pressure was rarely restored to normal Associated symptoms and signs of hypertension in general were favorably affected or at least remained un changed On continued administration there was no evidence of development of tolerance or idiosyncrasy to the drug

Patient and physician must co operate to establish a symp tom free therapeutic dosage schedule Moreover dosage re quirements may vary considerably from patient to patient so that only by cautious trial of increasing doses can the proper schedule be established The most satisfactory mode of ad ministration is by mouth after meals and at bedtime

Although V viride in present available forms is far from an ideal or curative medicinal agent in essential hypertension further investigation of purified products without objection able side effects is justified

Clinical Studies on Veratrum Alkaloids Action of Pro toveratrine and Veratridine in Hypertension Clinical use of veratrum alkaloids has fallen into disrepute mainly for two reasons Alkaloid content of the plant extracts vary greatly and reliable standardization methods are not available Vera trum causes severe toxic reactions such as nausea vomiting and unpredictable sometimes profound fall in blood pressure Despite these drawbacks certain obstetric clinics have con tinued to use Veratrum viride in eclampsia Recently there has been a revival of use of the drug in treatment of hypertension

Edward Meilman and Otto Krayer[4] (Harvard Univ) in

(4) C cul t 1 204 213 F b y 1950

tension after the initial fall in blood pressure Tetraethyl ammonium chloride and the adrenolytic benzodioxane drugs have also been recommended as test substances Both should lower high blood pressure caused by circulating epinephrine

Operation is not without danger There is an increased susceptibility to paroxysmal tachycardias and to auricular or ventricular fibrillation in the presence of excess epinephrine Patients often show a great rise in blood pressure when the tumor is being manipulated and a great fall after veins from the tumor are ligated For this reason adequate amounts of epinephrine and adrenal cortex extract should be available Possibly benzodioxane drugs could be used to prevent excessive rises in blood pressure due to manipulation of the tumor at operation

Veratrum Viride and Essential Hypertension are discussed by Robert W Wilkins[3] (Boston Univ) Although Veratrum viride has been used intermittently for more than a century in treatment of fever tachycardia and disturbances of the circulatory system in modern times its use has been generally discredited Recently however it has been tried clinically in essential hypertension with results favorable enough to stimulate physiologic studies of its hemodynamic effects in man

Hypotensive effects of V viride whether crude root purified extract or pure alkaloid are apparently similar in normal animals normal persons and hypertensive patients Generally vasodilator these effects may be mediated through the central nervous system Salivation nausea and vomiting are the most frequent of the unpleasant side effects circulatory collapse is the most alarming though usually innocuous evidence of overdosage of the drug As antidotes for these reactions atropine (0 5 1 0 mg) or ephedrine (30-45 mg) or both have been given intramuscularly During the hypotensive response to V viride cardiac output does not decrease but on the contrary may increase In no sense sympatholytic the drug leaves vasomotor reflexes and postural adaptations intact Although renal blood flow initially may decrease with the first appreciable fall in arterial pressure after administration of the drug it returns to control values when the pressure becomes stabilized at lower levels Although blood flow through the brain has not yet been measured clinical

(3) New England J Med 24 535 538 Apr 6 1950

In 168 trials with protoveratrine first degree heart block oc curred 4 times nodal rhythm 12 times ventricular extrasys toles 2 times bigeminy 2 times and Wenckebach phenomenon twice Arrhythmias appeared about 10-15 minutes after in jection and usually lasted a few minutes If the dose which produced arrhythmia was given simultaneously with atropine no arrhythmia appeared yet blood pressure did fall Pa tients who were fully digitalized showed electrocardiographic changes such as increased P R interval or bigeminy at lower doses of protoveratrine

With veratridine only slight or no fall in blood pressure or heart rate occurred at doses that produced nausea vomit ing and sweating except in one patient

It is concluded that protoveratrine in a dosage range caus ing satisfactory clinical circulatory effects has insignificant side effects or none at all Veratridine in the authors opinion scarcely warrants further clinical trial Upper range of dos age of protoveratrine for therapeutic application is not defi nitely established and it is an exceedingly toxic drug

Influence of Sodium Chloride on Actions of Desoxycorti costerone Acetate Attention has repeatedly been called to the fact that many toxic actions of desoxycorticosterone acetate (DCA) depend on sodium chloride content of the diet Exces sive dietary supplements of sodium chloride increase severity of the nephrosclerosis periarteritis nodosa and hypertension produced by DCA treatment whereas diets comparatively poor in sodium chloride tend to diminish these toxic reac tions Hans Selye Helen Stone Paola S Timiras and Carlos Schaffenburg[5] (Univ of Montreal) report an additional series of observations on rats receiving DCA while on a diet com pletely devoid of sodium chloride Experiments were per formed to determine whether dietary protection against DCA is absolute or relative and whether it extends to all actions of the corticoid or is limited to some of them

Unilaterally nephrectomized rats were divided into two groups One was untreated In each animal of the other group two 40 mg pellets of DCA were implanted All animals were given a synthetic sodium chloride free diet for four weeks At this time each group was divided in half and half the ani mals in each of the original two groups were given 1 per cent

(5) Am. H rt J 37 1009 1016 J 1949

jected protoveratrine intravenously 168 times in 26 hypertensive patients The highest single intravenous dose was 0 20 mg Veratridine was administered to 14 patients 17 times intravenously and 7 times intramuscularly

Fall in blood pressure produced by protoveratrine was essentially the same each time and was usually maximal in the first 10 15 minutes Results were similar in patients with renal hypertension and those with essential hypertension Amount of protoveratrine which caused a given fall in blood pressure varied from patient to patient In general doses of 1 μg/kg or less had little or no effect Above this level and up to 3 μg/kg there was increased response with increasing doses Larger doses were not tested Duration of action was variable but was usually one to three hours depending on dose as well as on the patient Fall in blood pressure was accompanied by a decrease in heart rate which could be abolished by atropine Response to the cold pressor test was not abolished during the hypotensive period following administration of protoveratrine In more than half of 40 experiments a moderate postural hypotension occurred affecting systolic level more than diastolic pressure

In every instance intravenous administration of a large enough dose of protoveratrine produced a subjective sensation of unusual warmth in the face mouth throat hands epigastrium perineum and feet which was not unpleasant and lasted 10 25 minutes With the highest doses given there was frequently slight dizziness aggravated by quick motions of head or eyes In five patients large doses caused a pressing choking sensation in the epigastrium and substernally with a tendency to deep sighing respirations Neither of the two patients with angina pectoris in the series experienced this substernal oppressive feeling after the drug however Five patients were given protoveratrine while suffering from headache One did not respond in two there was mild relief with fall in blood pressure and in two a severe headache was completely alleviated during the hypotensive period

Four of eight patients who had the pattern of left axis deviation with flat or inverted T_1 had reversion of T_1 to upright during the period of lowered pressure and a return of the upright T wave to a flat or inverted wave as the effect of the drug wore off and blood pressure rose to previous levels

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(5) Am H rt J 37 1009 1016 J 1949

saline to drink other animals remained on the sodium chloride free diet The experiment was continued for another five weeks at the end of which time moribund condition of DCA treated animals receiving saline made it necessary to terminate the study

Results showed that rats maintained on the sodium chloride free synthetic diet tolerated otherwise fatal doses of DCA Sodium chloride deficiency also prevented renal and cardiac enlargement nephrosclerosis myocarditis hypertension and periarteritis nodosa normally caused by excessive amounts of DCA however it did not prevent atrophy of the adrenal cortex and pituitary which results from overdosage with this corticoid

From these observations the authors conclude that sodium is essential for the renal and through the intermediation of the kidney for the cardiovascular actions of DCA

Production of Hypertension in Rat by Substituting Hypertonic Sodium Chloride Solutions for Drinking Water is reported by Leo A Sapirstein Wilbur L Brandt and Douglas R Drury[6] (Univ of Southern California) In three experiments systolic blood pressures were determined in 27 control rats and in 31 rats whose sole source of fluid was 1 5 2 5 or 2 per cent sodium chloride solutions for six weeks In animals watered with hypertonic saline solutions arterial hypertension developed after a latent period of one to four weeks Autopsy revealed this to be associated with hypertrophy of the heart and kidneys relative to body weight The authors concluded that substitution of hypertonic sodium chloride solutions for drinking water affords a simple inexpensive and dependable method of producing arterial hypertension in the rat

Importance of Dietary Protein, Calories and Salt in Experimental Renal Hypertension Philip Handler and Frederick Bernheim[7] (Duke Univ) report on data obtained in control experiments preliminary to studies of the significance of liver function in renal hypertension Purified synthetic diets were used in study of effects of various nutritional factors on blood pressure of adult male rats rendered hypertensive by subtotal nephrectomy Dietary levels of protein calories and salt

(6) P oc. Soc Exper B l & Med 73 8 85 Jan a y 1950
(7) Am. J Phy ol 160 31 40 January 1950

independently exerted a profound influence on systolic blood pressure.

Effect of protein was determined at three dietary levels all of which supported rat growth In rats ingesting diets of normal salt content systolic pressures were stabilized at the following levels high protein 168 mm medium protein 145 mm low protein 122 mm Addition of urea to a low protein ration exerted a slight pressor effect but not sufficient to account for the observed effects of dietary protein Addition of tyrosine and phenylalanine in amounts present in a 50 per cent casein diet had no effect on blood pressure

Restriction of daily food consumption to an amount just adequate for weight maintenance or very slow growth resulted in a fall to virtually normal pressures on all diets but that containing an unusually excessive amount of salt Drastic reduction of sodium content of the diet only slightly reduced systolic pressures of rats on high protein rations Addition of 3 per cent sodium chloride (10 times the normal level) to a low protein ration resulted in pronounced hypertension

It cannot be stated whether hypertension created in this fashion is analogous to any type of hypertensive disease known to occur in man In any case if results of this study are applied to management of hypertensive disease in man only qualitative concepts may be justifiably utilized

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CORONARY ARTERY DISEASE

Recent studies suggest that the ballistocardiographic technic may become a valuable adjunct in the diagnosis of angina pectoris Further investigations will be awaited with interest

The symptomatic benefit derived from coronary dilators is well known Although there is as yet no proof that these drugs have a beneficial effect in the disease by favoring the development of collateral circulation the clinical evidence is suggestive. A controlled study of this problem utilizing a large number of patients would be of much interest.

The last article in this chapter would suggest that when done cautiously and with due regard for the dangers of pulmonary edema intravenous infusion may be a valuable emergency measure in treatment of the state of circulatory collapse brought on by myocardial infarction —Ed

Ballistocardiographic Findings in Patients with Symptoms of Angina Pectoris are reported by Herbert R Brown Jr Marvin J Hoffman and Vincent de Lalla Jr[8] (Univ of

(8) Circulation 1 13 140 J[illegible], 195[illegible]

Rochester) A new aid in the diagnosis of angina pectoris is the ballistocardiograph an instrument which records waves arising from the heart beat itself when the pulse impact of ejected blood strikes the arch of the aorta pulmonary arteries and peripheral vessels

In a series of 50 patients 26 were thought to have typical angina pectoris and 24 atypical Patients were excluded from the series if they had symptoms of aortic stenosis aortic regurgitation hypothyroidism hyperthyroidism acute or chronic pulmonary disease anemia or arrhythmias or positive reactions for syphilis Abnormal ballistocardiographic changes were demonstrated in all 26 patients with typical angina pectoris 21 of whom had objective cardiac abnormalities and 5 of whom did not Of 24 patients with atypical angina pectoris 21 showed varying degrees of ballistocardiographic abnormality although only 11 of the 21 had one or more of the usual stigmas of cardiovascular abnormality The three remaining patients had no objective evidence of cardiac abnormality and had normal ballistocardiograms therefore they were thought to be in anxiety states Since in all but 3 of the 50 patients the clinical diagnosis of angina pectoris was supported by abnormal ballistocardiograms ballistocardiography is considered to be a helpful diagnostic aid especially in atypical cases

Because the duration of symptoms in atypical cases was 17 3 months compared to 39 2 months in typical cases it was inferred that many patients with coronary artery disease may have atypical complaints preceding the development of classic and easily recognizable symptoms A considerable number of patients may present no signs or symptoms although they may have a moderate degree of arteriosclerosis of the coronary arteries In this category is the patient who ultimately has an acute myocardial infarction but who never had a sick day or a pain in his life In supposedly healthy patients over 50 abnormal ballistocardiograms are not surprising considering the incidence of heart disease although other criteria may often be negative many asymptomatic or atypical patients should curtail activity The ballistocardiograph furnishes objective evidence of circulatory abnormality in such cases by revealing defective mechanical heart action

Blood Cholesterol Studies in Coronary Artery Disease are

reported by Morris F Collen[9] Abundant evidence has accumulated which shows that most patients with coronary artery disease have a sustained hyperlipemia In a series of 84 male patients with acute myocardial infarctions the average plasma cholesterol concentration was 297 mg/100 cc Fifty two per cent had cholesterol levels over 300 mg By contrast in 66 normal subjects (persons who were not overweight and showed minimal evidence of aging) the average cholesterol level was 249 mg and only 10 per cent had cholesterol concentrations over 300 mg In general patients who had had an acute myocardial infarction at a young age tended to have a higher plasma cholesterol level than those who had had an infarct late in life

Plasma Cholesterol Concentrations Following Ingestion of 5 Gm Cholesterol in Patients with Coronary Artery Disease Morris F Collen David De Kruif and Frederick Geier[1] measured plasma cholesterol and ester concentrations in patients while they were fasting and two and four hours after ingestion of a test meal consisting of 250 Gm fresh egg yolk (about 5 Gm cholesterol) Determinations were performed on 27 *normal adult males i e persons without evident* metabolic disorders and with a negative family history for coronary artery disease and on 53 male patients who had recently had an acute myocardial infarction and therefore presumably had coronary atherosclerosis

Criteria for a normal cholesterol tolerance test were (1) an initial fasting cholesterol level below 300 mg/100 cc plasma and a cholesterol ester level below 200 mg (2) changes in plasma cholesterol concentrations two and four hours after the test meal which did not increase above the fasting levels by more than 30 mg cholesterol or 20 mg cholesterol esters According to these criteria 60 per cent of the 27 normal adult males had normal tests Ninety per cent of the 53 male patients who had recently had an acute myocardial infarction had abnormal tests in that one or more of the above criteria was exceeded

Coronary Sclerosis as Symptom of Xanthomatosis Muller's Syndrome The assumption that an increased amount of cholesterol in blood is an important factor in pathogenesis of

(9) P m t Fou d M B ll 55 59 J ly 1949
(1) Ibid. pp. 60 66

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Comparative Studies of Effect of Some Vasodilators in Angina Pectoris are reported by Ebbe Nyman[3] (Karolinska Hosp Stockholm) Defective knowledge regarding the quantitative effect of the different vasodilator drugs in man under physiologic and pathologic conditions is partly to be explained by the lack of objective reproducible functional tests that has hitherto existed The calibrated and reproducible tests for cardiopulmonary function now available allow more satisfactory study of this question

The cardiopulmonary function test used in the present investigation consisted in measured work on a bicycle ergometer Moderate work of 600 kg/minute was used An electrocardiogram was made after four minutes work and again three minutes after work was concluded The various vasodilators were then given and time of appearance of pain during work on the ergometer under influence of the drug was compared with time of appearance of pain in a control test before medication The whole series of experiments was carried out within one month and the tests were made at the same time each day on a man 35 who had had angina pectoris pains with typical localization and radiation in connection with rapid walking running and bicycling uphill for about four years There were no physical or roentgen signs of organic heart disease or of sclerosis or thromboangiitis obliterans in peripheral vessels

Best effect both on duration of pain free working period and the ECG was obtained with administration of a drug with a rapid action shortly before start of the function test Nitroglycerin 0 5 mg orally doubled length of the pain free period and had a noticeably favorable effect on the ECG Theophylline with ethylenediamine 0 24 Gm administered intravenously also prolonged the pain free period considerably and the ECG was likewise influenced favorably Theophylline with ethylenediamine 1 8 Gm orally also had a good effect on the pain free period but effect on the ECG was not so striking Sorbide dinitrate 0 09 Gm by mouth prolonged somewhat the pain free period but did not cause any change in the ECG Papaverine hydrochloride 0 03 Gm intravenously improved the ECG but did not alter duration of the pain free period Procaine 0 30 Gm over the

(3) Acta med Scandina 131 565 570 1948

arteriosclerosis has been supported by experimental investigations in which rabbits fed cholesterol developed lesions of the arteries similar to those observed in human arteriosclerosis This experimental arteriosclerosis has a direct parallel in the systemic disease xanthomatosis which is associated with an increased amount of cholesterol in blood

Xanthomatosis is characterized by hypercholesteremia and abnormal cholesterol deposits in various organs especially in skin tendons and intima of arteries Cutaneous manifestations appear as flat or tuberous nodules Epidermis is always unaffected but the yellow color of underlying cholesterol deposits may be seen if skin is stretched On eyelids deposits appear as xanthelasmas Tendinous xanthomas are most often found on extensor tendons of fingers back of hands or below knuckles elbows tibial tuberosities and on the Achilles tendons Vascular deposits appear as typical atheromatous plaques in intima of aorta coronary arteries and larger arteries of the legs In advanced stages changes are macroscopically the same as in severe arteriosclerosis Xanthomatosis is a distinct hereditary disease apparently transmitted in a dominant way

Gunnar Welin (Gothenburg Sweden) describes a family of four brothers and three sisters six of whom showed pathognomonic external xanthomas between the ages of 29 and 47 Localization consistency and size of xanthomas of the different members showed a remarkable similarity All but one had symptoms of coronary sclerosis (angina pectoris) and two died of sudden cardiac failure In the two oldest brothers electrocardiograms showed changes significant of old posterior infarction The oldest brother died suddenly two months after examination autopsy showed a severe atheroarteriosclerosis which did not present any definite peculiarities The statement that it is impossible to differentiate between xanthomatous arteriosclerosis and arteriosclerosis of other origin at autopsy is thus confirmed Blood cholesterol was determined in five of the patients and two of their children All siblings and one of the children had definite hypercholesteremia with serum cholesterol values above 350 mg per cent

( ) Acta med Scand a 134 53 60 1949

more apt to experience greater hypotension and other unpleasant side effects The optimal dose for each patient was determined by beginning with small intravenous doses (50 or 100 mg) and working up to optimal dose

In this small series no conclusions could be drawn as to beneficial results other than symptomatic improvement However especially in patients for whom other methods of treatment proved inadequate the additional relief obtained with TEAC was gratifying

So called Silent Myocardial Infarction ' It has long been recognized that certain cases of myocardial infarction occur apparently without pain and that dyspnea is the predominant symptom and may overshadow the sensation of pain in the clinical picture Recently considerable evidence has indicated that prompt institution of anticoagulant therapy in acute myocardial infarction results in a diminished degree of morbidity and possibly also in a diminished mortality rate Hence ready recognition of forms of this disease in which pain is not a prominent feature has increased in importance Harold R Hipp James M Behrman and Howard E Heyer[5] (Dallas) attempted to determine conditions under which acute myocardial infarction might occur without readily recognizable evidences of pain and also to determine in such cases subjective symptoms other than pain which might indicate occurrence of the acute disease

Histories of 150 cases of recent myocardial infarction were reviewed and in 11 no history of pain had been obtained Diagnosis in 10 of the 11 cases was confirmed by autopsy a relatively acute infarction being found in each The eleventh case was confirmed by evolution of a pattern of typical electrocardiographic abnormalities

In the 11 cases the term painless proved to be a misnomer for in all there were factors which were probably sufficient to explain the absence of a history of pain The history was inadequate in five patients one was psychotic one in diabetic acido is two were in deep diabetic coma and one also in coma was found at autopsy to have a cerebral embolus A poor history i probably the commonest cause for absence of a history of pain Another patient complained of sudden onset of asthma with fever This probably represented onset of

(5) Am P t 4 64 66 O t be 1949

sternum prolonged the pain free period shifted the pain higher up and had some effect on the ECG

Results do not permit far reaching conclusions However one fact that emerges is that a sure effect is achieved only if the drug being tried is given in a readily absorbable form in immediate connection with the function test With the possible exception of sorbide dinitrate relatively small peroral doses of the drugs with a slower action did not seem appreciably to increase functional capacity

Tetraethylammonium Chloride in Treatment of Angina Pectoris William J Atkinson Jr[4] (St Louis Univ) gave tetraethylammonium chloride (TEAC) for 1 20 months to 28 patients with angina pectoris In 25 patients symptomatic improvement occurred judged by decrease in number of anginal and allied attacks weekly and by an increase in exercise tolerance Of those who improved 65 per cent had a significant decrease in number of attacks and 60 per cent a noticeable increase in exercise tolerance Psychogenic effects of the decided sensory stimulus obtained with TEAC intravenously seemed to play a part in these benefits However this was thought merely a contributory factor since only 1 of 11 patients did as well on other drugs which gave a sensory stimulus

Of the 28 patients treated 65 per cent were followed o 20 months No harmful effects attributable to administration of the drug were noted though most patients were over 60 and had either experienced a myocardial infarct before this study or had been in congestive failure at some time

Electrocardiograms of four patients taken before anginal attacks during an attack and two to four minutes after intravenous administration of TEAC showed an anginal pattern during the attack and reversion to the preanginal pattern immediately after administration of the drug Atkinson believes that TEAC actually breaks up the process involved in an anginal attack

Optimal dose of TEAC for treatment of angina pectoris varied greatly from patient to patient Responsiveness to the drug was usually increased by severe heart disease old age arteriosclerosis and some forms of hypertension If the dose was too large patients with one or more of these factors were

(4) Am. He t J 39 336-352 M h 1950

the shoulder may atrophy The term shoulder hand syn drome has been given to this form of reflex dystrophy The reflex is thought to start from an area of local tissue disturb ance such as a traumatized extremity myocardial infarct or cerebral lesion *Impulses from these areas set up a central* disturbance in the nature of a widespread continuous agita tion of the internuncial pool which spread steadily to stimu late anterior and lateral horn cells This incessant stimulation is expressed peripherally by motor and neurovascular symp toms Muscle spasm and vasomotor imbalance result and pro duce characteristic clinical features of the shoulder hand syndrome Treatment is repeated stellate ganglion infiltration with procaine

In group 2 pain is referred to neck shoulder and upper extremity without trophic changes There is no pain on mo tion nor is movement of the shoulder joint restricted Pain *is reflexly referred to* (1) *neck shoulder and proximal half of* the upper arm or (2) neck shoulder and entire upper extrem ity with burning tingling and a sensation of numbness in hand and fingers Shoulder and arm feel heavy and tired the dorsum of the wrist may become sore and gripping power of *the hand is often diminished Pain is usually worse at night* Diffuse tenderness may be present The clinical picture is that of scalenus anticus syndrome The authors present a case with these features

Man 61 had experienced recurrent mild epigastric pain radiat ing up to sternum and left shoulder 18 months previously Eight months previously he had been hospitalized for syncope Diagnosis was arteriosclerotic heart disease with cardiac enlargement coronary sclerosis and healed anterior myocardial infarct A second coronary attack occurred three months later Five months after the second attack the patient s chief complaint was pain in the left shoulder arm and hand particularly severe at night The left hand was numb and weak Examination revealed a tense tender scalenus anticus mu cle on the left Pressure on the lower end of the muscle above the clavicle caused severe pain which radiated to the shoulder arm and hand reproducing and intensifying the patient s symptoms In jection of the scalenus anticus muscle with 1 5 cc of 2 per cent pro caine caused the pain to disappear Tingling and numbness disap peared and strength of grip was restored There was slight recur rence of pain two weeks later and injection was repeated

The authors suggest that the mechanism of the scalenus anticus syndrome following a myocardial infarct is a sensori motor reflex mediated by the phrenic nerve When a myo

substernal tightness which is a common symptom of in farction of the myocardium Since pain is a subjective expe rience it is not surprising that it is interpreted in different fashions by different patients Three of the 11 patients were on the surgical service at time of the infarctions In all three administration of narcotics about the time when in retrospect it was thought that infarctions had occurred may have masked pain from the infarction Also it has been shown that pain in one part of the body actually raises the threshold for perception of pain arising in another area That a history of pain is frequently not obtained in patients in whom myo cardial infarctions develop after operation has been noted by many observers Two of the 11 patients complained chiefly of sudden onset of exacerbation of dyspnea and orthopnea and no history of pain was elicited during their hospitalization That manifestations of myocardial infarction may be chiefly those of congestive failure has been known many years How ever lack of history of pain is not necessarily synonymous with lack of pain In patients who have both pain and dysp nea dyspnea often seems to overshadow the sensation of pain and becomes the chief complaint Also the fact that many patients suffering from coronary artery disease characterize their distress as tightness or use some other unusual de scription of the sensation makes the unraveling of that symp tom from those of the complicating congestive failure difficult

From information gained from these 11 cases there is little to indicate that myocardial infarction is not essentially a pain producing lesion So many conditions may obscure pain in this disease that absence of a history of pain should not be taken to mean the patient did not have pain or that he would not have had pain had not his threshold of pain percep tion been altered

Possible Mechanism of Postcoronary Shoulder Pain has been investigated by Bernard D Judovich William Bates and Maurice S Jacobs[6] (Philadelphia) Reports indicate that the syndrome of painful *shoulder following coronary occlusion* can be divided into two groups In group 1 trophic disturb ances develop with changes resembling periarthritis of the shoulder joint and motion becomes painful and limited Re ferred pain may be causalgic or burning and structures about

(6) An J S g 8 216 219 A g t 1949

The first article separates sharply the only clinically important type of arteriosclerosis namely *atheromatosis* from a number of benign and incidental arterial diseases which are often confused with the more serious process A strong case is made for the importance of mechanical factors in determining the site of atheromatous change and of diet as a predisposing factor in atheroma It is becoming increasingly clear that the level *of blood cholesterol and apparently of certain lipoproteins of a special* molecular size is important in the production of atheroma The relative importance of total caloric intake fat intake and cholesterol intake as determinants of blood cholesterol remains in dispute The possibility that the plasma concentration of certain lipoproteins with a specific migration velocity rather than that of cholesterol is responsible for the tendency toward atheromatous degeneration is exciting and further studies will be awaited with interest —Ed

Causes of Arteriosclerosis According to William Dock[8] (Long Island College of Medicine) hardening of the arteries occurs in four different ways One way consists of atrophy of the media and replacement of muscle and elastic fibers by collagen which occurs as a diffuse symmetrical process producing wide long tortuous vessels such as are seen on the temples of many persons soon after they become adult and which become increasingly visible with age This change causes no decrease in lumen and hence does not produce vascular accidents or insufficiency The second way hardening of the arteries occurs is by aortic mucinous degeneration cystic degeneration or medial necrosis which commonly precedes dissecting aneurysm and occurs more often in hypertensive *hypothyroid subjects than in others The third way is by* regenerative intimal thickening in arteries supplying tissues which decrease in bulk and functional activity with age This change is part of the vascular atrophy of disuse and is most *striking in ovaries after the menopause and in brains in which* disseminated focal cortical atrophy occurs because of neuronal involution and death The fourth way is by the intimal change which causes all of the clinical manifestations of *arteriosclerosis* atheroma formation or atherosclerosis Because atheromas have been shown to be rich in cholesterol and have been produced in rabbits by feeding cholesterol there has grown up an impressive body of evidence that this lesion is due to deposition in the intima of cholesterol and its

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(8) B ll New Y k A d M d 26 182 188 M h 1950

cardial infarct takes place the resultant pericarditis irritates the sensory endings of the phrenic nerve This in turn causes an intrasegmental reflex reference of pain in the neck shoulder girdle and proximal half of the upper arm If stimuli are adequate a spasm of the anterior scalenus muscle develops as a reflex possibly axonal in mechanism Symptoms are then referred to the lower arm and hand by a reflex scalene spasm superimposed on the primary source of pain

Plasma and Blood Infusion Following Myocardial Infarction John J Sampson and Isadore M Singer[7] (San Francisco) gave 30 intravenous infusions of blood and normal human plasma to 11 patients exhibiting one or more shock like episodes after acute myocardial infarction Whereas only 1 of the 11 patients recovered and was discharged asymptomatic results of the infusions appeared to have carried four patients over critical periods of hypotension and they died later of secondary infarction or heart failure

No apparent harmful effects of infusion of blood or plasma were demonstrated except in a single patient with a high initial venous pressure Infusions seemed to be more effective when systolic blood pressure was under 85 mm Hg They were likewise more effective when given before four hours after severe hypotension developed and at rates of at least 2 and preferably 2 5 5 ml minute

It is assumed that use of blood or plasma infusions probably cannot alter the immediate destruction of the myocardium by ischemia and that death will follow such destruction when it is extensive However the favorable effects may be due to (1) reduction of effects secondary to shock (improved irrigation of the coronary bed) (2) maintenance of normal or excess venous return to the heart to preserve cardiac output in the presence of the dilated left ventricle (3) reduction of the area of dilatation of the myocardium surrounding the infarcted zone a process which may possibly cause or increase the shocklike symptoms and hypotension

It cannot be predicated that all the successful results in this study were due to infusions since spontaneous recovery from hypotension after myocardial infarction is common However prompt response in most instances seemed conclusive evidence of a genuine therapeutic effect

(7) Am Heart J 38 54 68 July 1949

Africa remains unanswered The high cholesterol content of diets was thought to be a factor but in three separate studies in America no relation could be found between blood cholesterol and the cholesterol content of diets The importance of obesity in causation of atherosclerosis however has been well demonstrated Over most of the world want is the rule and atherosclerosis is being prevented where luxurious diet prevails atherosclerosis flourishes

Role of Lipids and Lipoproteins in Atherosclerosis Though some workers claim that most patients with atherosclerosis show a significant elevation in blood cholesterol level a considerable number have levels in the accepted normal range John W Gofman Frank Lindgren Harold Elliott William Mantz John Hewitt Beverly Strisower Virgil Herring (Univ of California) and Thomas P Lyon[9] (San Jose Calif) therefore undertook a physicochemical investigation of the giant molecules of serum which may be composed of cholesterol its esters phospholipids fatty acids and protein as building blocks The basic premise was that it is possible that a defect might exist in certain of these giant molecules which could be responsible for development of atherosclerosis whereas the mere analytic levels of any of the building blocks in serum might be of little or no significance

The serum of normal rabbits showed a lipoprotein which ultracentrifugally appeared as a single component of flotation rate between 5 and 8 Svedberg units under the experimental conditions used When these rabbits were fed 3 Gm cholesterol a week an increase in concentration of the previously existing 5 8 S_f component occurred and several new components of S_f class 10 30 appeared The number of new components appearing in the serum of individual rabbits varied from none to all despite the fact that the maintenance ration of cholesterol was the same for all animals When autopsy was done on rabbits after 15 weeks of cholesterol feeding it was found that those rabbits failing to develop high levels of the components of S_f greater than 5 8 units showed no gross atherosclerosis whereas mild to severe atherosclerosis developed in those with high concentrations of molecules of the S_f 10-30 class The observation that all rabbits attained comparable levels of the 5 8 S_f component but showed widely varying

(9) S 111 166 171 F b 17 1950

esters and to the resulting mild foreign body type of granuloma formation and scarring Thus it is similar to xanthoma which develops in the skin of persons with elevated blood cholesterol levels Dock believes that every patient with xanthoma has atheromas

Local factors in connective tissue are thought to play a large role because xanthoma and atheroma are focal lesions with an obvious predilection for certain sites the upper lids being the commonest location for xanthoma and the aorta near its bifurcation and the coronary arteries being the preferred site for atheroma There is striking evidence that atheromas develop only when the ratio of cholesterol to phospholipid exceeds a certain level Xanthomas form rapidly when the plasma cholesterol levels are high they never form when the blood cholesterol is 160 mg per cent or less Cholesterol precipitates in areas of necrosis hemorrhage or simple degeneration of the intercellular matrix So far however, there is little evidence that such degeneration or injury precedes cholesterol deposition *in skin* Xanthomas appear where connective tissue is in constant motion or vibration The anterior mitral leaflet and the epicardial parts of the coronary arteries usually the first sites of atheroma formation are also in constant motion A striking example is in arteriovenous fistula in which the artery leading to the leak shows far more atherosclerosis than the corresponding vessel on the opposite side of the body In such an artery the thrill or vibration due to flow of high velocity is greater than normal Thickness of the intima seems to be important also Coronary arteries have a far thicker intima than mesenteric or radial arteries and far more atheromas The rate at which plasma filtrate is forced into the intima is thought to depend on arterial pressure Atherosclerosis is definitely correlated with level of arterial pressure in both systemic and pulmonic circuits Tibial arteries have far more severe sclerosis than radials and the aorta at its bifurcation may be one confluent mass of advanced atheromas when the arch is the site of only a few small plaques Pulmonic hypertension predisposes to pulmonic atherosclerosis

The question of why atheromas appear in Europeans and North Americans even though they are normotensive and free from endocrine disease and not in the people of Asia or

Cholesterol Metabolism in Health and Disease Its Relationship to Arteriosclerosis is summarized by L N Katz J Stamler and L Horlick[1] (Michael Ree e Hosp) Cholesterol metabolism is difficult to analyze because of the ubiquity of cholesterol and the complexity of its exogenous endogenous circulation Detailed solution must await intermediary metabolic studies in vitro and in vivo such as have been carried out with carbohydrate metabolism Tracer methodology *utilizing isotopes must be extensively applied to this problem* With this technic it has been shown that cholesterol is the parent substance of physiologically important steroids such as cholic acid and progesterone Presumably steroids of the adrenal cortex are also synthesized from the cholesterol molecule Tracer studies have proved synthesis of cholesterol from acetate Cholesterol homeostasis may also be studied by means of a tolerance test similar to that used for glucose

Plasma total cholesterol levels in normal persons show a wide variation from 107 to 320 mg /100 cc which is not significantly affected by age sex national or ethnic origin or climate Apparently normal diet also has no effect but this is still in dispute It has been shown that there is a complex plasma lipoprotein moiety involving all lipid constituents in relatively fixed proportions In normal postabsorptive plasma the lipid aggregates (chylomicrons) are 1 2 μ in size and the plasma is a clear limpid solution Disturbance of concentration and balance of lipids may lead to milky plasma (chylomicronemia) Lipid particles are less finely dispersed and their colloidal stability is less well protected This condition occurs physiologically after a fatty meal It is present in a number of pathologic states and has been implicated in pathogenesis of arteriosclerosis Ultracentrifuge studies indicate that atherosclerosis may be correlated with plasma level of particular low density cholesterol bearing lipoprotein molecules Presumably alterations in plasma lipid protein complexes lead to the ready precipitation of insoluble cholesterol and its esters either extra or subintimally Cholesterol esters remain entrapped in the arterial wall and by virtue of their irritant properties provoke growth of fibrous tissue and atheroma

Etiology and pathogenesis of nephrotic hypercholesteremia

(1) Am P ct. 1 461 468 M y 1950

degrees of atherosclerosis suggests that this component is not implicated On the other hand correlation between development of severe atherosclerosis and presence in the blood of high concentrations of components of the S_f 10 30 class suggests that at least some of these components either are the molecules which deposit in atheromatous plaques or are a reflection in the blood of the metabolic abnormality which results in cholesterol induced atherosclerosis

Studies in man showed the incidence of measurable concentrations of molecules of the S_f 10 20 class to be significantly higher in males aged 20-40 than in females of the same age group Both males and females over 40 showed significant increases in the incidence of measurable concentrations of molecules of this class compared with corresponding younger age groups A higher incidence was found in diabetics than in normal persons of corresponding age groups Of 104 patients with proved myocardial infarction 101 showed presence of molecules of the S_f 10 20 class in measurable concentrations All these observations are considered compatible with the hypothesis that elevated serum concentration of these molecules is associated with development of atherosclerosis

Preliminary study of 20 patients whose diet was restricted in cholesterol and fats demonstrated that concentration of S_f 10 20 class of molecules was definitely reduced or even brought down to a level below resolution intracentrifugally in 17 within two weeks to one month

Comparison of blood cholesterol levels with presence or absence of molecules of the S_f 10 20 class revealed that although there is a general trend toward increased frequency of occurrence of such molecules in serums with cholesterols over 200 mg per cent this was by no means a universal finding It was quite common also to find serums with cholesterol levels well below 200 mg per cent with appreciable or high concentration of molecules of the S_f 10 20 class Further it was common to find serums with cholesterol levels well over 200 mg per cent without any measurable concentration of molecules of this class These facts are thought to explain why previous workers have been unable to reach definite conclusions concerning atherosclerosis by studying analytic cholesterol values

sis in man suggests that weight loss might account for the effectiveness of some procedures in preventing experimental atherosclerosis J B Firstbrook[2] (Univ of Toronto) investigated this possibility in the rabbit by examining the relation between weight changes produced by various levels of food intake and the severity of experimental atherosclerosis

TECHNIC —After preliminary observation for at least one week on Ralston Purina Rabbit Chow Checkers fed ad lib male rabbits of various breeds and unknown age were weighed and sorted on the basis of similar body weight into pairs or groups of three One animal in each group was allowed chow ad lib The other member of a pair was offered 50 per cent of the previous day s food intake of the freely fed animal The other two members of the groups of three were restricted to 60 and 40 per cent maximal intakes After two weeks on the restricted feeding schedule daily administration by stomach tube of 1 Gm cholesterol daily seven days a week was begun After four to seven weeks cholesterol administration animals were killed and studied at autopsy

As expected there was a highly significant correlation between food intake and final weight In the absence of control of the other variables degree of atherosclerosis was not significantly correlated with cholesterol dosage with initial weight or with weight change Under conditions of this experiment variations in total cholesterol dosage had little effect

The authors conclude that in evaluation of agents suspected of influencing experimental atherosclerosis in the rabbit and probably in other species there must be statistical or experimental control of changes in body weight The low incidence of experimental atherosclerosis in rabbits rendered diabetic with alloxan before cholesterol administration is probably associated with characteristic emaciation of these animals rather than with a specific effect of the diabetes

Vascularization of Aorta Comparative Study of Aortic Vascularization of Several Species in Health and Disease J Schlichter and R Harris[3] (Michael Reese Hosp) using an injection technic studied the vascularity of the ascending aorta in the dog human chicken and rabbit roentgenologically and microscopically Results indicated that vascularity of the ascending aorta is comparatively greatest in the dog and decreases progressively in man the chicken and rabbit Species differences in number and distribution of vasa vaso

(2) S 3 31 33 J n. 13 1950
(3) Am J M S 218 610 615 D mber 1949

are unknown It is thought that the kidney plays an active role in lipid metabolism but specific aspects await elucidation Likewise cholesterol and thyroid hormone are intimately related physiologically but mechanisms of interaction are obscure Experimental feeding of large amounts of cholesterol has produced hypercholesteremia and atherosclerosis in certain species Lipotropic factors such as choline inositol methionine or lipocaic prevent fatty livers but do not consistently prevent hypercholesteremia and atherosclerosis

Plasma and tissue lipid pattern of cholesterol fed chicks is duplicated in man with primary xanthomatosis Unlike experimental cholesterol induced lipidosis however this essential hypercholesteremia of man usually does not respond to a low fat diet or to lipotropic factors Victims of this disorder often succumb at an early age to coronary artery disease Atherosclerosis in diabetic subjects is thought to be secondary to hypercholesteremia The completely depancreatized diabetic dog exhibits marked hyperlipemia and hypercholesteremia A fatty liver develops Insulin abolishes the hyperlipemia but the fatty liver persists Addition of raw pancreas to the diet cures the fatty liver and restores plasma lipids to normal

In experiments with chicks the authors have shown that the degree of atherosclerosis is proportional to the amount and duration of cholesterol feeding They were unable to influence development of atherosclerosis by use of lipotropic substances It was possible with increased cholesterol intake to produce atherosclerosis despite minimal hypercholesteremia Desiccated thyroid was of value against cholesterol induced atherosclerosis in chicks but was ineffective in eliminating spontaneous atherosclerosis Action of thyroid was thought to be a specific effect on cholesterol and lipid metabolism the nature of which remains to be worked out

Obviously there are tremendous gaps in knowledge of cholesterol metabolism its disturbances and its relation to arteriosclerosis Since degenerative vascular disease is a principal cause of disability and death the closing of these gaps is of major concern

Effect of Changes in Body Weight on Atherosclerosis in Rabbit. Evidence that a caloric intake in excess of energy requirement is associated with a high incidence of atheroslero

There was a wide spectrum of histologic changes resulting from prolonged cholesterol feeding ranging from increase in ground substance of the intima of the aorta with infiltration of sudanophile material to very extensive foam cell plaques hyaline and cartilaginous metaplasia and heavy deposits of calcium in granules and plates Cessation of cholesterol feeding was followed by fibrotic changes in lesions of both the thoracic and abdominal portions of the aorta by disappearance and diminution of foam cells and fat and by calcification of atheromatous abscesses Scavenger like fat filled cells were also noted in the intima

Controls showed few gross lesions but many microscopic ones Scattered focal deposits of sudanophile material were seen in the intima and inner portions of the media of the thoracic aorta In the abdominal aorta spontaneous lesions were characterized by fibrosis of the intima with sudanophile deposits and calcium granules at the intimal medial junction

Relationship of Atheromatosis Development in Chicken to Amount of Cholesterol Added to Diet Arteriosclerosis of a type closely resembling that found in man appears spontaneously with advancing age in birds The chicken possesses certain advantages for research in this field because atherosclerotic lesions can be induced in a relatively short time and the induced lesions resemble the spontaneously occurring ones in many respects Furthermore the chicken normally ingests cholesterol containing food Spontaneous arteriosclerosis develops in the chicken at age 5 6 months at the earliest arteriosclerosis is found in 45 per cent of chickens over 1 year old It is obvious therefore that the chicken is a suitable animal for experimental production of atherosclerosis if used before age 6 months when spontaneous arteriosclerosis begins to occur

L Horlick and L N Katz (*Michael Reese Hosp*) *under*took to quantitate effect of various concentrations of dietary cholesterol on the rapidity and degree of development of atherosclerosis in the chicken Feeding of cholesterol in concentrations of 0 5 1 2 and 4 per cent of the diet for 5 10 and 15 weeks was investigated

Results showed a direct relationship between concentration of cholesterol in diet and frequency and severity of

(5) Am H t J 38 336 349 S ptembe 1949

rum were unrelated to size of the aorta since vascularity of the smaller dog aortas was superior to that of the larger adult human aortas whereas aortas of premature babies generally showed better vascularization than those of rabbits and chick ens of approximately similar size

These basic differences in blood supply in different spe cies may explain some of the difficulty in producing medial necrosis or arteriosclerosis in dogs and the ease with which these changes are produced in rabbits Correlation of the present findings with previous observations indicates that species with better vascular supply to the aortic wall have less tendency to develop degenerative arterial lesions whereas species with poorer vascularity exhibit a greater tendency

The hypothesis is suggested that development of degen erative arterial lesions appears to vary inversely with the blood supply to the arterial wall This hypothesis does not preclude the probability that other factors may play a role but emphasizes the importance of the blood supply factor

Retrogression of Atherosclerotic Lesions on Cessation of Cholesterol Feeding in Chick. Louis Horlick and Louis N Katz[4] (Michael Reese Hosp) investigated the effects of ces sation of cholesterol feeding on the hypercholesteremia and atherosclerosis resulting from moderate periods of cholesterol feeding

Prolonged feeding of a diet containing 2 per cent choles terol in cottonseed oil to chicks for 24 weeks resulted in pro gressive elevation of blood cholesterol levels There was in creasing severity of atherosclerosis for 15 weeks then a level ing off and a further increase in severity during the last 2 weeks of the experiment Cessation of cholesterol feeding after 10 weeks caused a rapid decline in blood cholesterol levels to normal within 3 weeks There was also a gradual regression in severity of lesions over 14 weeks It appeared that early lesions could be completely resorbed on cessation of cholesterol feeding whereas more severe lesions under went regressive and reparative changes There was little dif ference in rate of regression or disappearance of the aortic lesions in birds placed on a normal mash diet and those placed on a low fat cholesterol free diet after cessation of cholesterol feeding

(4) J Lab & Clin Med 34 14 7 1442 Octobe 1949

medial necrosis or other degenerative lesions and so did not have the local ischemia or degeneration on which atheroma might be expected to develop Lesions in the two animals with atheroma were confined to the area of interference with the vasculature of the vessel wall Six dogs whose aorta was not cauterized were kept on a similar regimen of cholesterol and/ or thiouracil They showed no atheromatous or other patho logic changes of the aorta The authors conclude that nour ishment of the blood vessel walls may be one important factor in atheromatosis

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CONGESTIVE HEART FAILURE

A number of recent studies have emphasized the importance of sodium deficiency consequent to prolonged dietary re triction or to the injudicious use of mercurial diuretics It should be remembered that a patient may have an excess of extracellular fluid with edema in one part of the body and have extracellular fluid depletion in the remaining portions The symptoms and management of this common disorder are indicated in one of the following articles —Ed

Experimental Hypervolemic Heart Failure Its Bearing on Certain General Principles of Heart Failure In a group of experiments by William Huckabee Gus Casten and T R Harrison[7] (Southwestern Med College) dogs were infused rapidly with large volumes of fluid Atrial and femoral venous pressures rose steadily during infusion cardiac output rose to a peak and then dropped The gradient of pressure along the veins decreased progressively during infusion These ex periments indicated that the hemodynamic defect in primary hypervolemic heart failure is the heart s inability to respond to an increasing filling load beyond a certain point

From considerations concerned with the flow of fluids through tubes the authors conclude that the diameter of veins has more influence than venous pressure on volume flow and that the intact animal differs from Starling s heart lung preparation in that in the former peripheral resistance is variable and the diameter of the veins may vary This con clusion was illustrated by experiments in which only a rough correlation existed between venous pressure and cardiac out put The authors suggest that the concept of inflow load in

(7) C cul t 1 343 356 M h 1950

atherosclerosis which resulted There was also a relation between duration of the feeding period and degree of atherosclerosis produced for each concentration of cholesterol in the diet With concentrations of cholesterol above 0 5 per cent increasing the feeding period beyond 10 weeks did not appear to increase the amount of atherosclerosis Atherosclerosis occurred as early as two weeks after beginning the diet Early occurrence of atherosclerosis was related to an enormous increase in blood cholesterol level which occurred during the first week of cholesterol feeding Amounts of cholesterol over 0 5 per cent produced much the same degree of hypercholesteremia suggesting that there was an upper threshold for assimilation of cholesterol There was a semi direct relationship between degree of lipemia and degree of atherosclerosis found

Occurrence of Atheromatous Lesions after Cauterization of Aorta Followed by Cholesterol Administration is described by J G Schlichter L N Katz and J Meyer[6] (Michael Reese Hosp) Disturbances in the vascularity of the aortic wall cause disease of the aorta In the dog obstruction of the vasa vasorum of the ascending aorta leads to medial necrosis and its sequelae aneurysm formation dissecting aneurysm and spontaneous rupture The tendency toward atheroma formation is thought related among other things to the state of the vasa vasorum Vasa of the dog are extremely well developed and this may be one reason for the known difficulty in producing atheromatosis in this animal In the present study on dogs therefore some of the vasa vasorum were destroyed and hypercholesteremia was superimposed for months The effect of this combination of procedures was analyzed at autopsy

The ascending aorta of eight dogs was cauterized In one atheroma developed within 20 weeks on being given cholesterol orally and intraperitoneally In a second dog atheroma developed within 12 weeks on the same regimen plus thiouracil orally In a third dog atheroma failed to develop after 10 months on cholesterol and thiouracil orally Three other dogs (two given cholesterol only and one cholesterol and thiouracil) lived less than five weeks postoperatively apparently not long enough for atheroma to develop The other two (one given cholesterol only and one thiouracil only) did not show

(6) Am J M Sc 218 603 609 December 1949

Energetodynamic Cardiac Insufficiency, discussed by Robert Hegglin[8] (Univ of Zurich) is characterized by a considerable lengthening of the QT space of the electrocardiogram associated with a shortening of the Q second heart sound interval verified on the phonocardiogram which is the expression of a prematurely interrupted ejection period This syndrome is caused directly by a disturbance of the metabolism of the myocardium the contraction of which becomes weak

Clinically this disturbance appears in all pathologic conditions accompanied by hypopotassemia consequently in paroxysmal paralysis and grave and persistent diarrheas it is reversible and disappears completely after recovery from *hypopotassemia But it appears also in many other pathologic* conditions and thus acquires more clinical importance It is found in diabetic coma and in hypoglycemia in which there is probably also hypopotassemia because the potassium metabolism is nearly always disturbed in these manifestations in porphyria hyperthyroidism severe infections (pneumonia scarlet fever diphtheria and even some grave anginas) severe intoxications (barbiturates veratrine)

Diagnosis is easily made from the ECG and analysis of the heart sounds In pronounced cases auscultation reveals the short interval between the first and second heart sounds The heart is not dilated or deformed Prognosis is good when the cause is removed at the opportune moment however death may be caused by the syndrome in the previously mentioned diseases

Since the syndrome is always found as a secondary complication of a general disease treatment must first be aimed at the primary disorder therefore the hypopotassemia must receive careful attention Administration of 1 5 Gm potassium chlorate by mouth corrects the situation in most cases

Surgical Treatment of 'Cardiac Lung' Ligation of Inferior Vena Cava and/or Tricuspid Valvulotomy To restore equilibrium between the two ventricles Pedro Cossio and Isidro Perianes[9] (Buenos Aires) have devised two operations One is intended to drain blood from the pulmonary venous system toward some sector of the systemic circulation by

(8) C d l g 15 65 77 1949
(9) J A M A 141 772 776 J ly 2 1949

corporating venous pressure and venous diameter should supplant that of venous pressure as the stimulus to changes in stroke output of the heart

Actual flow into the ventricle was thought to depend on the relation between inflow load and ventricular diastolic pressure Thus a decline in the latter function may occur when diminished peripheral resistance leads to increased systolic emptying and under such circumstances increased inflow and output occur with constant inflow load If ventricular diastolic pressure rises inflow load must increase to keep inflow and output the same In addition a rise of ventricular diastolic pressure occurs as a consequence of incomplete emptying of the ventricle and excessive residual blood This may occur not only when cardiac output is low but also when it is high It is suggested that the only hemodynamic disturbance constant to all types of heart failure is a reduction of cardiac output relative to inflow load

Hypervolemia may be either primary and a cause of cardiac failure or much more commonly secondary and a result of heart failure In states of myocardial failure rise in ventricular diastolic pressure necessarily results in a distributional shift of blood from the peripheral toward the central portions of the venous system

On the basis of these considerations the authors suggest the following physiologic classification of heart failure and other circulatory disturbances disorders of cardiac filling disorders of cardiac emptying and mixed types Disorders of cardiac filling include (1) deficient inflow (shock) (2) excess inflow with or without adequate systolic emptying (thyrotoxicosis anemia beriberi arteriovenous fistula acute nephritis and rapid infusions) and (3) mechanical interference as in pericarditis mitral stenosis and rarely ball valve thrombi or auricular tumors Cardiac emptying may be decreased because of (1) increased resistance (acute cor pulmonale aortic stenosis coarctation or hypertension) or (2) decreased myocardial function from cardiac arrhythmias or myocardial infarction or from inflammatory or degenerative myocardial disorders Mixed types include (1) unequal filling and emptying of separate heart chambers in valvular heart disease and (2) deficient filling and emptying of the heart in sodium depletion

lotomy failed in only one case in which the attempt was abandoned because of sudden collapse while the instrument was in the heart Two hours later the patient completely re covered but died a month later during an attack of pulmonary edema In each of the other four patients the operation proved relatively simple and venous pulse became positive and un dulating The patients were definitely improved one of them surviving the operation five months

TECHNIC—A hollow metal rod 2 3 mm in diameter and 30 cm long with a shallow hook at one end and a Hamilton manometer at the opposite end is inserted through a small incision in the jugu lar vein When the instrument enters the auriculoventricular orifice pulsations registered by the manometer increase in amplitude and as soon as it has passed through the orifice there is further sudden increase Once it has reached this position the instrument is gently advanced until resistance is encountered from the right ventricular wall then the instrument is turned outward and is drawn back to engage the chordae of the external cusp If they are successfully en *gaged resistance is experienced Firm traction of the instrument* sections whatever has been engaged by the hook The same pro cedure is repeated two or three times until a systolic murmur is heard to the right of the sternum The hook is then carefully with drawn

When the inferior vena cava was ligated above the venae hepaticae all animals died in one to three days of infarctions in the bowels and liver Ligation just below the renal veins gave satisfactory results Though the first attempt in a hu man being met with failure because of the patient s serious heart condition subsequent attempts brought both systolic and diastolic pressures down to normal and they remained so during two months the length of observation

Auricular Fibrillation without Other Evidence of Heart Disease Cause of Reversible Heart Failure Edward Phillips (Los Angeles) and Samuel A Levine[1] (Poston) investigated some of the changes in dynamics of the circulation that ap pear to develop as a result of auricular fibrillation in patients who have no other evidence of heart disease Their purpose was to emphasize that the arrhythmia alone can cause con gestive heart failure The clinical evidence also suggested that some cases of irreversible heart failure with auricular fibrillation may have started with an essentially sound heart and that the subsequent disability might have been prevented

(1) Am J M d 7 478 489 O t be 1949

end to end anastomosis of a large pulmonary vein with the axillary artery the splenic vein or the azygos vein The second is directed to reduction of the right ventricular output either by tricuspid regurgitation following a tricuspid valvulotomy or by reduction of the return of venous blood to the right side of the heart by ligation of one of the main veins

Drainage of pulmonary venous blood into the systemic circuit was not feasible however in experimental animals because pulmonary vein pressure was lower than systemic vein pressure Though pulmonary venous pressure is undoubtedly elevated in patients with heart failure another difficulty that precluded this operation in human beings was the large thoracotomy wound and prolonged general anesthesia which would not have been tolerated by patients in an advanced stage of cardiac disease On the other hand both tricuspid valvulotomy and ligation of the inferior vena cava were well tolerated Both procedures attained the contemplated objectives reduction in volume of right ventricle output subsequent decrease of the passive congestion of the lungs and consequently improved left ventricle efficiency identical with the effect of venesection but giving more lasting results Ligation of the inferior vena cava was a much more serious operation than tricuspid valvulotomy since it required a general anesthetic and produced postoperative disorders However it was more effective for the following reasons the surgeon could see what he was doing the operation was in itself a prophylactic measure against pulmonary embolism which so often causes death and it overcame the 50 per cent increased output caused by supine posture For half a century it has been known that lesions of the tricuspid valve far from aggravating a mitral lesion exerted a healthy effect thereon In the authors opinion surgery for the medically uncontrollable cardiac lung should begin by ligation of the inferior vena cava and be followed by tricuspid valvulotomy unless there are extensive vascular obstructions in the limbs that would render the first operation useless In mitral stenosis it is probably most satisfactory to undertake valvulotomy initially

Tricuspid valvulotomy was carried out in five patients four of whom had uncontrollable heart failure The fifth though relatively healthy was suffering from recurrent attacks of pulmonary edema despite intensive treatment Valvu

It is concluded that auricular fibrillation per se may produce cardiac dilatation and progressive congestive failure in patients with otherwise normal hearts This is a truly reversible type of heart failure There is reason to believe that a considerable number of patients with auricular fibrillation cardiac enlargement and congestive failure (that eventually becomes irreversible) have little or no organic heart disease The authors believe that regularization of the rhythm with quinidine in the early stages may prevent progressive heart failure and in the latter stages may be curative

Clinical Report on Toxicity of New Mercurial Diuretic (Thiomerin®) for Subcutaneous Administration Considerable effort has been directed toward developing a mercurial diuretic which is systemically less toxic than those previously used locally nonirritating and readily administered Recently the disodium salt of N(γ carboxymethylmercaptomercuri β methoxy) propyl camphoramic acid (thiomerin®) has been introduced for subcutaneous use This compound shows chemical similarity to mercurophylline (mercuzanthin®) but the theophylline has been replaced by sodium mercaptacetate with the formation of a mercaptide Cardiac toxicity in experimental animals has been reported to be about 1/160 that of other mercurials given intravenously

Alan R Feinberg Julien H Isaacs and William S Borkan[2] (Univ of Illinois) report clinical experiences with thiomerin® Two groups were studied 59 hospitalized patients and 350 outpatients seen at intervals of one to four weeks The clinic group consisted entirely of patients with various degrees of congestive heart failure most of the hospitalized group were also in congestive failure Thiomerin® was administered subcutaneously in doses of 0 5 3 cc equivalent to 0 07-0 42 Gm of the compound or 0 02 0 12 Gm mercury The most common dose was 1 cc Hospitalized patients received 1 35 injections at intervals of one to three days clinic patients 1 25 injections at intervals of one to four weeks as determined by response

Results were evaluated by weight loss and clinical improvement Achievement of dry weight was used as a measure of effective diuresis Diuresis was satisfactory in the outpatient group Dietary co operation was found necessary

(2) Am J M S 218 298 301 Sept mbe 1949

if normal rhythm had been restored by use of quinidine in early stages of the arrhythmia

Of the 84 patients studied all with auricular fibrillation of unknown etiology and no evidence of organic heart disease 61 had permanent fibrillation and 23 had transient fibrillation Forty seven patients were studied carefully before and after reversion of the arrhythmia with quinidine Six had pro nounced congestive failure another patient who did not re spond to quinidine also had congestive failure Seven others had latent congestive failure

The most common symptom of those without failure was palpitation In the group with failure there were the custom ary features of dyspnea orthopnea and an enlarged liver Transverse diameter of the heart averaged 14 4 cm during fibrillation and 14 3 cm after reversion in 20 patients with out frank failure Transverse diameter in four with congestive failure averaged 17 4 cm during and 15 4 cm after auricular fibrillation In six patients the P R interval was slightly pro longed after reversion One of these reverted spontaneously without any medication Four patients showed transient in version of T waves after reversion one of which reverted spontaneously without medication Vital capacity of lungs in 28 patients without failure averaged 3 448 cc during fibrilla tion and 3 700 cc after reversion In the group with failure the vital capacity increased from 2 575 to 3 725 cc Arm to tongue circulation time in 11 patients without failure averaged 24 seconds during auricular fibrillation and 20 seconds after regularization Venous pressure in 13 patients without failure averaged 107 mm H_2O during fibrillation and 97 mm after reversion

Regularization after quinidine therapy occurred in 88 5 per cent and there were no untoward complications In those who did relapse the normal rhythm persisted for an average of 26 9 months Average duration of regular rhythm in patients under 50 who relapsed was 61 4 months in those over 50 it was 21 months Nineteen patients had not relapsed and still had regular rhythm after 2 months to 21 years Maintenance of regular rhythm was much longer in these patients than in those with organic heart disease which was reverted In the group with advanced congestive failure responses were dramatic all symptoms disappearing after regularization

Thirty five ambulatory patients attending the clinic for severe congestive heart failure were given mercaptomerin sodium whenever a mercurial diuretic was clinically indicated The subcutaneous route was effective in removal of edema prevention of accumulation of edema and maintenance of the patient s state of compensation In this regard it was as satisfactory as the previously used diuretics given intravenously or intramuscularly

Thiomerin[*] was given to 73 hospitalized patients with the severest degree of chronic congestive heart failure In general diuretic response to the drug administered subcutaneously was as satisfactory as that to the previously used mercurial diuretics either intramuscularly or intravenously Local reactions were usually not clinically significant and none of the patients refused continuation of therapy because of local irritation

The authors concluded that mercaptomerin is an effective and safe diuretic which may be administered subcutaneously to advantage Predictability of a satisfactory diuretic response and degree of diuresis achieved are similar to those with intravenous use of mercurophylline injection Mercaptomerin sodium by subcutaneous injection is superior to other mercurial diuretics administered intramuscularly

Renal Failure Associated with Low Extracellular Sodium Chloride Low Salt Syndrome With the wide use of low salt diets in congestive heart failure and hypertension and with the often excessive use of dextrose in water for postoperative care renal insufficiency from the low salt syndrome may be more frequently observed Since it is usually unrecognized unless looked for specifically and since adequate replacement therapy will often alter an otherwise fatal outcome Henry A Schroeder[4] (Washington Univ) describes 21 cases of the condition and methods for its treatment

Development of the low salt syndrome was recognized by (1) successive depression of urinary volume occurring during three to five days (2) depression of urinary chlorides to negligible quantities (which did not increase after injection of mercurial diuretics) (3) rapid progressive gain in weight (4) elevation of nonprotein nitrogen content of the blood (5) fall in plasma levels of chloride and sodium and (6) occasionally an elevation of cardiac rate Symptoms complained

(4) J A M A 141 117 124 S pt 10 1949

for maintenance of dry weight In 56 of the 59 hospitalized patients diuresis was equal to or better than that to be expected from other diuretic agents

Generalized toxic reactions were absent except for occasional development of muscle cramps fatigue and weakness resulting from too rapid depletion of electrolyte and water Local immediate and delayed irritative reactions occurred but were minimal

The authors concluded that thiomerin® administered by the subcutaneous route is an effective diuretic agent Absence of all but minor local irritative phenomena the apparent complete absence of systemic toxicity and the ease of administration provide definite advantage

Subcutaneous Administration of Mercaptomerin (Thiomerin®) Effective Mercurial Diuretic for Treatment of Congestive Heart Failure A mercurial diuretic which overcomes many of the objections inherent in the currently available preparations is known as mercaptomerin sodium (thiomerin® sodium) Not only is cardiac toxicity decreased but the amount of local irritation at site of injection is minimized to such a degree that the preparation is relatively painless on subcutaneous injection

Robert C Batterman David Unterman and Arthur C DeGraff[3] (New York City) studied the effectiveness and safety of mercaptomerin for treatment of congestive heart failure according to several plans First an effort was made to compare predictability of an effective diuretic response to intravenous or subcutaneous injection of the drug with that to an intravenous injection of mercurophylline For this purpose 45 hospitalized patients with varying degrees of congestive heart failure were given the diuretics when preliminary control periods indicated that sufficient time had elapsed to evaluate concomitant therapeutic measures From data on predictability of satisfactory diuresis that is a 3 lb weight loss mercaptomerin administered subcutaneously was decidedly satisfactory *Predictability of response whether patients received mercurophylline intravenously mercaptomerin intravenously or the latter subcutaneously* was identical Urinalyses after administration of the diuretic revealed no abnormality in any patient

(3) J A. M A 140 1 68 1271 A g 0 1949

cumulation of edema fluid was estimated at about 8 kg Intravenous *injection of 2 cc. mersalyl and theophylline solution caused urinary* excretion of 17 Gm. chloride calculated as sodium chloride Three days later the same dose resulted in excretion of 6 1 Gm and urinary volume was progressively diminished ending finally in oliguria. A later injection of 4 cc mersalyl and theophylline solution did not affect urinary water or chlorides As the patient was ingesting only 1 Gm salt/day excretion of 23 1 Gm salt (395 m Eq) accompanied by only 2 2 kg water apparently depleted the extracellular electrolytes A week later she had retained 3 4 kg water which further hydrated and diluted the electrolytes She died of renal and cardiac insufficiency

Reversible features of the low salt syndrome either from spontaneous remission or therapy with salt suggest that it is a state of renal insufficiency dependent on low plasma levels of sodium and chloride The diuretic and nitrogen lowering action of hypertonic saline solution has sometimes been dramatic as in the following case

Man 67 with arteriosclerotic heart disease severe ascites and edema lost over 500 m Eq chloride in urine in 10 days as a result of mercurial and xanthine diuretics Characteristic symptoms and signs appeared and urinary output diminished. Transfusion of whole *blood did not initiate diuresis nor did use of 5 per cent dextrose* intravenously Probably the latter only served further to dilute the electrolytes But intravenous injection of 255 m Eq salt (16 Gm.) apparently restored electrolyte balance sufficiently to allow diuresis to begin In four days urinary output increased to well over 1 L however chloride output of urine remained exceedingly low and symptoms disappeared Although he had gained 2 9 kg in weight diuresis initiated by salt resulted in loss of this amount and a further loss of 1 kg

Of the 21 patients with the low salt syndrome 10 died and 11 recovered In most of the fatal cases terminal renal insufficiency was considered only in retrospect Injection of hypertonic sodium chloride solution was not accompanied with adverse symptoms when plasma electrolytes were low Venous pressure was measured simultaneously and usually there was no change Presence of pulmonary congestion did not contraindicate injection of hypertonic sodium chloride

The mechanism by which lowered electrolytes contribute to renal insufficiency is unknown Theoretically if adequate water is available and plasma is being filtered by glomeruli normal kidneys should be able to excrete water and retain salt until electrolyte balance is restored The abnormal (hypertensive cardiac or aged) kidney may be deficient in some

of were (1) drowsiness weakness and lethargy (often wrongly attributed to sedatives) (2) loss of appetite sometimes with thirst (3) nausea and occasional vomiting (4) occasionally abdominal and muscular cramps and (5) the secondary symptoms of an increase in extracellular fluids when edema was already present In every patient observed there was some degree of organic renal disease usually without renal insufficiency or a functional renal disturbance such as that associated with congestive failure

Therapy was aimed at rapid restoration of concentration of sodium and chloride in extracellular fluids to relatively normal levels by intravenous injection of hypertonic solution of sodium chloride (5 or 6 per cent) Since the problem in these patients was overhydration because extracellular fluid contained an amount of sodium chloride insufficient to maintain normal osmotic equilibrium the most rapid method of restoring concentrations of sodium and chloride to normal was to administer salt without water Experiments showed that intravenous administration of 5 or 6 per cent sodium chloride solution could be tolerated if given slowly the venous pressure rising only slightly if at all Although salt can be given orally the amount usually necessary to restore electrolyte equilibrium may be large (20-40 Gm) can produce gastrointestinal disturbances and may have an erratic rate of absorption The amount of sodium chloride given depended on calculation of the deficit in plasma in estimated interstitial fluids and in accumulated edema Normal extracellular fluid volume was considered 20 per cent of body weight Edema fluid if present was roughly estimated from gain in body weight Plasma levels of chloride and carbon dioxide combining power were followed daily subsequent injections of salt were based on these values Usually when plasma level of chloride reached 90-95 m Eq / L diuresis was well established As a rough approximation for a 70 kg man 17 1 m Eq of sodium chloride (1 Gm) should be expected to elevate plasma levels 1 m Eq /L if edema is not present and salt is not excreted

Development of the low salt syndrome is illustrated by the following case

Woman 30 had subacute and chronic rheumatic endocarditis with involvement of mitral and tricuspid valves Extracellular ac

vania Hospital, 1937-47, Inclusive was made by Joseph B Vander Veer and P T Kuo[6] (Philadelphia) Of 26 628 pregnant women delivered during this period 409 had heart disease Types of heart disease were in approximately 80 per cent rheumatic in 12 per cent hypertensive cardiovascular in 4 per cent congenital Of the 409 patients 31.3 per cent were given digitalis at various periods before during and after pregnancy There were 14 maternal deaths (mortality rate of 3 4 per cent) among the 409 patients Heart failure was directly or indirectly responsible for 10 deaths Seven patients with rheumatic heart disease died between the seventh and eighth month of pregnancy and three died in the first 48 hours of puerperium Acute infections were the cause of death in 7 of the 14 patients precipitating acute congestive failure in 4 There were 54 fetal deaths (13.2 per cent) prematurity was the commonest cause Approximately 50 per cent of patients were delivered by use of low forceps during the second stage of labor Major operative procedures were rarely performed on patients with rheumatic heart disease unless there were gynecologic indications

Systolic murmurs of grade 1 intensity are of little significance during pregnancy especially if best heard in the pulmonic area If the patient gives a history suggestive of previous rheumatic infection and the murmur exceeds grade 1 in intensity a diagnosis of potential heart disease should be made Such murmurs can best be diagnosed after delivery however frequent examination of heart and lungs during pregnancy and labor should be made to determine the functional capacity of the patient Decompensation is most often manifested by elevation of respiratory rate tachycardia and appearance of moist rales at lung bases Pulse rates exceeding 110/minute and respiratory rates above 24/minute indicate onset of acute heart failure

With the possible exception of patients with coarctation of the aorta all patients functionally in class 1 and most in class 2 may be allowed to undertake pregnancy Patients functionally in classes 3 and 4 with or without a previous history of decompensation and those with auricular fibrillation should be advised against undertaking pregnancy If such patients are pregnant when first examined and have not passed the

(6) Am Heart J 39.216 J ry 19 0

functions Whether the low salt syndrome occurs only with renal disease or renal functional disturbance cannot be stated at this time Return of renal function probably does not depend on restoration of circulatory efficiency through increases in blood volume for venous pressure was not reduced during anuria Nor does it depend on adequate levels of blood pressure The hazards of rigid restriction of sodium chloride in diets of cardiac patients used concomitantly with mercurial diuretics cannot be overemphasized

Use of Potassium Chloride and "Digoxin" in Congestive Heart Failure Because many cases of poisoning have resulted from the use of purified glycosides of digitalis in the treatment of heart disease and because damaged myocardiums are known to be deficient in potassium I E Buff[5] (Charleston W Va) tested the value of potassium therapy in patients with congestive heart failure The results were satisfactory Therefore 40 patients were treated with combined potasium and digoxin therapy (digoxin is a pure digitalis glycoside which is excreted with moderate rapidity)

Eighteen of the 40 patients had symptoms of digitalis poisoning when they were first seen They were given 5 10 Gm potassium chloride in milk orally or by intubation When the patient recovered from digitalis toxicity a maintenance dose of 1 0 Gm potassium chloride in milk was given three times daily for one week Then administration of the smallest dose of digoxin which would maintain digitalization was begun The remaining *22* patients were in failure but had not previously been digitalized They were given 0 5 mg digoxin and 1 0 Gm potassium chloride three times daily until a definite level of therapeutic digitalization was obtained After digitalization maintenance doses of digoxin and potassium chloride were established

The response of these patients to combined therapy was good Potassium seemed to enhance the action of digoxin and toxicity did not occur Under other regimens especially in older age groups mental depression and lack of co operation are noticeable but with this therapy patients were alert and co operative

Cardiac Disease in Pregnancy Study of Patients with Heart Disease at Philadelphia Lying In Division of Pennsyl

(5) South M J 42 1037 1040 Dec mber 1949

colored cinematographs of the auricles of the intact dog s heart at speeds up to 2000 frames/second Projected at 8 frames/second motion of the auricles was slowed 250 times A magnifying lens enlarged the auricle 100 or more times The *auricular contraction* wave was actually seen for the first time in this way Over 75 000 ft of film from experiments on over 200 dogs have been studied Arrhythmias were produced by aconitine and by postelectric stimulation methods A dual beam cathode ray oscillograph was used in some experiments and in others multiple channel electrocardiographic studies were used

It was concluded that all types of auricular arrhythmia (premature extrasystoles paroxysmal tachycardia flutter and fibrillation) arise from a single focus and that circus movement does not occur When a drop of 0 2 per cent solution of aconitine in benzene was placed on a small area of the wall of the auricle auricular fibrillation usually resulted after a few minutes When the ectopic focus was cooled by spraying with ethyl chloride the rhythm often changed in the following order from auricular fibrillation to flutter auricular tachycardia and sinus rhythm with auricular premature systoles When cooling was stopped and the point of application of aconitine was allowed to come toward body temperature a return of arrhythmias in reverse order was usually observed

Mechanism of Auricular Flutter and Fibrillation Topical administration of aconitine as a subepicardial injection of a dilute solution or an application of a few crystals on the epicardial surface of any part of the exposed auricle of a dog causes in a few minutes the appearance of a regular auricular tachycardia with rates of approximately 300 beats/minute Often the injection of aconitine causes an auricular fibrillation to appear David Scherf and Rosario Terranova[8] (New York Med College) continued their investigations of this phenomenon to accumulate further evidence that the aconitine tachycardia actually represents auricular flutter and not a tachycardia peculiar to the drug

Studies showed that auricular fibrillation could be transformed into auricular extrasystoles and flutter by slowing of the rate of stimulus formation with cooling the site of application of aconitine Cessation of the cooling led to reappearance

(8) Am J Phy 1 159 137 14 O t b 1949

fourth month of pregnancy abortion is indicated Thereafter conservative management is usually advisable Close observation adequate bed rest strict control of diet and sodium chloride intake and judicious use of digitalis usually maintain these patients in compensation through pregnancy and labor The earliest signs of heart failure are an indication for administration of digitalis Cesarean section and hysterotomy are usually not indicated in patients with rheumatic heart disease with failure but are frequently helpful in patients with hypertensive cardiovascular disease with pre eclampsia and eclampsia Lightening of the circulatory load during the last few weeks of pregnancy accounts for the relatively rare occurrence of acute cardiac failure in the last month of gestation In most patients with heart disease surgery is not recommended because the mortality rate has been demonstrated to be much higher when operative procedures are used

ARRHYTHMIAS

Because of its lifesaving value in paroxysmal ventricular tachycardia quinidine is often considered the drug of choice for paroxysmal auricular tachycardia Actually digitalis intravenously in the form of lanatoside C is usually to be preferred Because treatment of the two conditions differs an electrocardiogram should always be taken when there is doubt as to which condition is present

Two of the following articles offer strong evidence against the validity of the classic hypothesis that the circus movement is the basic mechanism responsible for auricular flutter and auricular fibrillation —Ed

Mechanism of Auricular Arrhythmias Since the classic studies of Lewis on the nature of auricular arrhythmias little has been published on the subject He believed that auricular flutter is due to a regular circus movement in the auricles which sweeps around the openings of the venae cavae He attributed auricular fibrillation to a circus movement of the same general type but the impulse was thought to pursue a tortuous and redundant path Paroxysmal auricular tachycardia was attributed to a rapidly discharging ectopic focus in the auricle

For three years Myron Prinzmetal Eliot Corday Isidor C Brill Alvin L Sellers Robert W Oblath Walter A Flieg and H E Kruger[7] (Univ of California) have been taking

(7) C cul tion 1 241 45 F b a y 1950

they were frequently accompanied by substernal pain sudden collapse shock dyspnea or syncope The immediate prognosis was good because in all but a few patients normal rhythm was resumed following appropriate therapy The ultimate prognosis was not good in those who had underlying coronary or valvular disease however a fair number of these were able to carry on a useful occupation for years In persons with no organic heart disease prognosis was generally excellent However even in this group sudden death may occur death during a paroxysm occurred in one patient who had a structurally normal heart at autopsy

The treatment of choice for paroxysmal ventricular tachycardia is quinidine therapy Oral administration was successful in 46 of 57 episodes In patients seriously ill intravenous administration was successful in 20 of 31 attacks In 13 patients magnesium sulfate given intravenously was occasionally of value in 2 potassium salts given orally were of no value in 1 intravenous administration of morphine was of no value

It is concluded that the intelligent use of quinidine is of great value in this condition and frequently saves the life of the patient

Supraventricular Paroxysmal Tachycardia in Infants and Children is discussed by Stanley Gibson[1] (Northwestern Univ) The cause of paroxysmal tachycardia in infancy is obscure It may occur at any period during infancy but is likely to arise during the first few weeks of life The symptoms include restlessness and irritability poor response to feedings frequent vomiting ashen gray color with the possible appearance of distinct cyanosis as the attack progresses The respiratory rate is alarmingly increased and may reach 150/minute Because of rapid breathing and chest noises cardiac auscultation may be difficult The rapid heart rate alone furnishes the clue to diagnosis the rate is regular practically always above 200/minute and may be in excess of 300 As the attack progresses the liver enlarges and edema of the lower extremities may occur Unless rapid heart action is interrupted by therapy the course may be steadily downhill with fatal termination In this respect paroxysmal tachycardia in infancy differs from that commonly seen in older children and adults in whom the attack eventually subsides even without

(1) M Cl N rth Am 34 217 222 J y 1950

of flutter and when the rate of stimulus formation again increased fibrillation appeared

During auricular flutter stimulation of the vagus nerve and cooling of the site of aconitine application were used simultaneously The flutter was abolished by the cooling and when it reappeared the rate slowly increased without any change of the form of auricular waves The long distance between P waves could not be explained by presence of a circus mechanism Occasionally stimulation of the vagus nerve during auricular flutter caused long pauses between the auricular waves this also spoke against presence of a continuous circulating wave

At the beginning of the action of aconitine a sinus tachycardia appeared and was inhibited by stimulation of the vagus later auricular flutter suddenly appeared and its rate increased during stimulation of the vagi From this it is concluded that two different types of stimulus formation were being dealt with The hypothesis is advanced that during auricular flutter there is a constant stimulus and the response of the auricle to this stimulus depends only on the length of the refractory phase

Paroxysmal Ventricular Tachycardia Study of 107 Cases is reported by Charles A Armbrust Jr and Samuel A Levine[9] (Harvard Univ) Patients were aged 13 83 however most were 50 70 Diagnosis was often suspected by simple bedside examination but was confirmed by electrocardiographic studies Clinically an occasional case was overlooked because only one heart sound could be heard to each cardiac cycle and the rate was estimated to be only one half of its actual value

In 79 patients (74 per cent) the underlying cause of heart disease was coronary artery disease generally with recent or old myocardial infarction Nine patients had rheumatic heart disease 13 no heart disease and 6 miscellaneous conditions There were 27 patients who had recurrences of prolonged attacks over a course of months or years the duration varying from hours to 24 days Digitalis seemed to play a role in the precipitation of paroxysmal ventricular tachycardia in only a small number of patients

Although attacks of tachycardia were often symptomless

(9) Circulation 1 840 January 1950

they were frequently accompanied by substernal pain sudden collapse shock dyspnea or syncope The immediate prognosis was good because in all but a few patients normal rhythm was resumed following appropriate therapy The ultimate prognosis was not good in those who had underlying coronary or valvular disease however a fair number of these were able to carry on a useful occupation for years In persons with no organic heart disease prognosis was generally excellent *However even in this group sudden death may occur* death during a paroxysm occurred in one patient who had a structurally normal heart at autopsy

The treatment of choice for paroxysmal ventricular tachycardia is quinidine therapy Oral administration was successful in 46 of 57 episodes In patients seriously ill intravenous administration was successful in 20 of 31 attacks In 13 patients magnesium sulfate given intravenously was occasionally of value in 2 potassium salts given orally were of no value in 1 intravenous administration of morphine was of no value

It is concluded that the intelligent use of quinidine is of great value in this condition and frequently saves the life of the patient

Supraventricular Paroxysmal Tachycardia in Infants and Children is discussed by Stanley Gibson[1] (Northwestern Univ) The cause of paroxysmal tachycardia in infancy is obscure It may occur at any period during infancy but is likely to arise during the first few weeks of life The symptoms include restlessness and irritability poor response to feedings frequent vomiting ashen gray color with the possible appearance of distinct cyanosis as the attack progresses The respiratory rate is alarmingly increased and may reach 150/*minute Because of rapid breathing and chest noises* cardiac auscultation may be difficult The rapid heart rate alone furnishes the clue to diagnosis the rate is regular practically always above 200/minute and may be in excess of 300 As the attack progresses the liver enlarges and edema of the lower extremities may occur Unless rapid heart action is interrupted by therapy the course may be steadily downhill with fatal termination In this respect paroxysmal tachycardia in infancy differs from that commonly seen in older children and adults in whom *the attack eventually subsides even without*

(1) M Cl N rth Am ca 34 217 22 J ry 1950

specific measures to break the abnormal rhythm Moreover measures usually employed in older patients such as massage or compression of the carotid sinus pressure on eyeballs induction of vomiting quinine quinidine pilocarpine or physostigmine are rarely effective in infants However digitalis is often effective Digitalis was used successfully in all but 2 of 12 patients

If symptoms are not alarming and there is no vomiting digitalis may be given by mouth 50 mg initially followed by 25 mg at four hour intervals Normal rhythm is sometimes established in 24 hours but two or three days of therapy may be necessary If symptoms and signs are more severe digitalis in similar or even larger doses may be given intramuscularly In two infants whose condition was so grave on admission that digitalis would probably not have acted with sufficient rapidity to save life acetylcholine bromide intravenously produced a prompt response One infant required only 1 mg but a total of 7 mg was necessary in the other

Paroxysmal tachycardia in childhood is less serious than in infancy and may respond to a variety of therapeutic measures Digitalis and/or quinidine are usually successful when simpler measures fail

Treatment of Paroxysmal Supraventricular Tachycardia with Lanatoside C J Gordon Barrow[2] (Atlanta Ga) treated 26 patients with paroxysmal supraventricular tachycardia which was refractory to vagus stimulation with lanatoside C intravenously Usually injection of an initial dose of 1 2 mg was done in 60 120 seconds If rhythm had not reverted to normal in 30 minutes 0 4 mg more was given in the vein In one case a third dose of 0 4 mg was necessary before the rhythm was controlled but in all other patients arrhythmia was stopped by 1 2 1 6 mg of drug Lanatoside C proved non toxic and relatively free from unpleasant side effects Barrow believes it is the drug of choice at present for treatment of the acute attack of paroxysmal supraventricular tachycardia

(2) Ann I t Med 3 116 119 J y 1950

ELECTROCARDIOGRAPHY AND OTHER PROCEDURES

The idea that electrocardiograms are useful only in primary diseases of the heart is erroneous Actually the tracings may be of suggestive value in such diverse conditions as myxedema famılial periodic paralysis and changes in the concentration of certain electrolytes It is al o important to realize that emotional disturbances many drugs and the process of aging may produce electrocardiographic changes in the absence of clinically important heart disease It cannot be emphasized too strongly that opinions based on electrocardiograms alone without integration with the entire clinical picture are likely to lead to grave diagno tic errors

The electrokymograph although still in the developmental stage and largely a research tool is beginning to offer information of clinical value Angiocardiography is proving of increasing value in detection of the various types of congenital cardiac disea e but is not without danger It is a s mpler technic than cardiac catheterization The relative hazards of the two procedures and the comparative value of the information yielded by them are as y t uncertain —Ed

Electrocardiographic Observations during Cardiac Catheterization are reported by I Ralph Goldman S Gilbert Blount Jr Allan L Friedlich and R J Bing [3] Although over all mortality in cardiac catheterization reported from various laboratories is low (0 1 per cent) certain complications may arise during the procedure—primarily cardiac arrhythmias recognition of which is important

The authors made electrocardiographic observations throughout cardiac catheterization in 50 patients One or more types of cardiac arrhythmia developed in all but one patient Auricular premature systoles occurred in 60 per cent nodal premature systoles in 78 per cent supraventricular tachycardia of auricular or nodal origin in 28 per cent and auricular flutter in 6 per cent Ventricular premature systoles occurred in 86 per cent and short bursts of ventricular tachycardia in 78 per cent Ventricular flutter was seen in 6 per cent Ventricular fibrillation developed in one patient during cardiac catheterization with a fatal outcome Various degrees of auriculoventricular block occurred in 8 per cent of patients and transient right bundle branch block in 12 per cent

With one exception withdrawal of the catheter resulted in cessation of the serious arrhythmias encountered Therefore prompt recognition of appearance of an arrhythmia is of great importance This may best be accomplished by continuous

(3) B ll J h H pk Hosp 86 141 168 M h 1950

electrocardiographic observation during cardiac catheterization

Differentiation of Changes in Q-T Interval in Hypocalcemia and Hypopotassemia A Carlton Ernstene and William L Proudfit[4] (Cleveland Clinic) describe electrocardiographic findings in a typical case of hypocalcemia and in five cases of hypopotassemia due to various causes

Earliest effect of a low serum potassium content consisted of rounding and broadening of T waves T waves generally but not always decreased in amplitude also Q T interval was frequently prolonged and whether or not this change occurred was determined entirely by the degree to which duration of T waves was increased RS T segments were not lengthened but were often slightly depressed Duration of QRS complexes was increased occasionally Prominent U waves commonly appeared in limb leads and lead CF_4 and by partial fusion with the descending limb of the T waves sometimes caused further apparent lengthening of Q T interval

In contrast to findings in hypopotassemia the electrocardiographic pattern of hypocalcemia was simple and consisted entirely of prolongation of the Q T interval due to lengthening of the RS T segment

Hyperpotassemia and Electrocardiographic Changes in Uremia J Wener and N K M de Leeuw[5] (Montreal) made electrocardiograms and took specimens of blood for chemical analyses at repeated intervals of five patients with uremia In one patient the final ECG s were obtained at the instant of death and in two others ECG s and serum for potassium determinations were obtained within one hour before death

The earliest electrocardiographic abnormality noted was elevation of the T wave which was especially apparent in lead CF_4 Peaked T waves were not always increased abnormally and in some instances only a slight elevation occurred which if taken alone without a previous tracing for comparison was well within normal limits T wave changes became apparent at serum potassium concentrations of 23 7 28 8 mg per cent At concentrations of 28 8 mg per cent and above depression of the S T segment with diphasic or inverted T

(4) Am. H t J 38 260 72 A g t 1949
(5) Canad. M A J 61 406 412 O tobe 1949

waves was noted P waves disappeared at serum potassium levels of 33 2 mg per cent and above Widening of QRS com plexes indicating intraventricular block was observed at serum potassium levels of 33 2 mg per cent and complete disintegration of the entire QRS complex terminating in cardiac arrest was noted in the terminal tracing in one patient at a serum potassium concentration of 54 9 mg per cent

Severe renal insufficiency as evidenced by high nonprotein nitrogen and creatinine values was present in all five patients However there was no correlation between degree of non protein nitrogen and creatinine retention in blood and serum potassium concentration There was close correlation between potassium retention and volume of urine excreted Elevations of serum potassium levels were noted only in the presence of persistent oliguria or almost complete anuria Hypochloremia was present in only one patient Serum sodium concentration determined in only one patient was slightly below normal Serum calcium concentration varied from 6 05 to 9 63 mg per cent none of the patients showed any symptoms or signs of tetany Neurologic disturbances such as paresthesia weak ness or flaccid paralysis reported in some cases of hyper potassemia were absent

Order of T Wave Changes in Exercise Electrocardiograms Urs Straumann[6] (Basel) used a method for measured exercise with the patient recumbent to eliminate clinostatic influences due to changes from the erect to the prone position Tests were made with an ergometer attached to the foot of the pa tient s bed and manipulated with the arms The friction gen erated by moving the hand grips warmed copper plates set between wooden blocks From the temperature difference spe cific heat and size of the copper plates the calories created by effort were measured and converted into kilograms The load of exercise was divided into four grades increasing from 120 to 1 200 or more kg

Results of the tests were tabulated in percentage deviation from the resting average in each case

Ten healthy subjects aged 22 28 were given tests and showed striking lowering of T waves after effort of grades 3 and 4 which lasted about 1½ minutes or less depending on the energy expended The initial rise in T waves observed by

(6) C d log 15 86 110 1949

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(4) Am Heart J 38 260 72 August 1949
(5) Canad M A J 61 406-412 October 1949

cardiographic abnormalities which at least superficially resemble those produced by organic myocardial disease The commonest abnormalities are displacements of the S T segment from the isoelectric line and lowering or inversion of T waves Since it seemed that suggestion of emotional states to a person under hypnosis might result in similar abnormalities Leslie L Bennett and Norman E Scott[7] (Univ of California) experimented on five normal persons In all five tachycardia was produced In one when emotional states of anxiety and anger were suggested the ECG showed definite T wave abnormalities In this person the procedure was as follows

PROCEDURE—Hypnosis was induced While the person was going to sleep he was told that all bodily sensations would disappear Tachycardia was then produced by suggestion After tachycardia was established the person was told of it and that he could do nothing about it even if he wished Then he was told that his helplessness made him angry—angry to the extent that his anger encompassed both himself and the hypnotist Immediately thereafter he was reassured and given suggestions for relaxation and sleep Three standard leads were taken during the periods of hypnotic sleep anxiety and anger and deeper sleep Additional control ECG s were made when the person was not hypnotized

The ECG s made during hypnotic sleep did not differ significantly from the control ECG however the ECG made during a period when anxiety was suggested showed definite deviations The most important abnormalities were accelerated rate lowering of T_1 and lowering or disappearance of T_2 and T_3 These electrocardiographic changes occurred 2 3 minutes after suggestions of anxiety the tracing reverted to normal within 60 90 seconds after the person was reassured There was a striking similarity between these abnormalities and those due to organic heart disease

Results of this experiment indicate that a diagnosis of cardiac disease in a patient should not be made from an ECG alone without relating it to the whole clinical picture

Study of Electrocardiogram in Persons over 70 Changes in the electrocardiographic scheme of elderly persons have been described a number of times but there has been no agreement as to the frequency of abnormal records R J McNamara[8] (Charleston W Va) attempted to determine incidence of abnormal ECG s in elderly persons without cardiac

(7) Am. P t. 4 189 190 Dec mb 1949
(8) G t 4 150 160 M y J 1949

other investigators was not noted and Straumann believes this to be due to absence of clinostatic influences

The second group tested comprised 31 patients 3 of whom had electrocardiographic signs of myocardial damage They reacted to grade 1 exercise with decided lowering secondarily of T waves Of six patients with questionable cardiac disease two reacted normally the other four had definitely lowered T waves after grade 1 exercise Twenty two patients gave no evidence of cardiac insufficiency but their histories suggested that the myocardium might be overstrained Two of them had a primary rise and three a secondary lowering of T waves which was more pronounced than in normal subjects Six patients in this group showed primary lowering of T waves whereas 11 reacted normally

Healthy subjects had maximal secondary lowering of T waves averaging 17 per cent after grade 1 40 per cent after grade 2 and 3 and 53 per cent after grade 4 exercises A brief summary of three cases reported by Straumann gives an idea of what happens to T waves (1) A cardiac patient had a primary rise of T wave height 55 seconds after grade 1 effort but a secondary lowering of 20 per cent in 7 10 minutes On grade 2 exertion there was a marked primary rise followed in three to five minutes by a secondary lowering of 40 per cent of resting T wave height (2) A hypertensive patient reacted to grade 1 exercise with a secondary lowering of 30 per cent (3) A patient with bronchopneumonia and negative findings on the ECG showed an insignificant primary lowering but a rather high secondary lowering of T waves after grade 2 exercise This was a borderline case

It is shown that exercise tests with constant observation of T waves give information about the adaptability of the heart muscle to physical effort The time element is important in T wave interpretation for in the first 15 seconds the changes are rapid and primary lowering may even off in 30 seconds

Straumann compares his results with those reported by others

Production of Electrocardiographic Abnormalities by Suggestion under Hypnosis Case Report There has been increasing recognition that anxiety states fear neurocirculatory asthenia hyperventilation syndrome etc may cause electro

enlargement and hypertension Patients selected for study were presumably normal from a cardiac standpoint at all standards except electrocardiographic there were 78 men and 22 women aged 70 and over who were receiving no cardiac medication and who were without significant cardiorespiratory symptoms Auscultation revealed no diastolic murmurs and no systolic murmurs of more than faint or moderate intensity Blood pressure was 160/90 or under A teleroentgenogram showed heart size to be within normal limits No patient gave a history of substernal effort pain or of previous severe chest pain suggestive of coronary occlusion

Abnormal ECG s were found in 30 per cent The commonest abnormalities were premature contractions T wave changes low voltage of QRS complex and intraventricular conduction defects Thirty one per cent had only minor changes of indefinite significance such as premature contractions low voltage or P wave irregularity and 39 per cent had a normal ECG Electrocardiographic abnormality became more frequent with increasing age in the second half of the eighth decade but essentially normal outnumbered abnormal ECG s in persons over 80 Incidence of abnormal ECG s was higher among men

Electrocardiogram in Familial Periodic Paralysis Familial periodic paralysis is a rare disease characterized by recurrent attacks of quadriplegia which usually occur at night and are associated with a low serum level of potassium Harold N Perelson and Richard S Cosby[9] (Los Angeles) report electrocardiographic findings in two cases of familial periodic paralysis and discuss their diagnostic value

Man 25 was hospitalized during an attack of familial periodic paralysis Electrocardiograms revealed a moderate degree of sagging of RS T segment in lead I and depression of RS T take-offs in leads II and III In lead CF_4 the RS T take off was depressed and there was pronounced sagging of the RS T segment Q T was 0 6 second which with heart rate of 75/minute indicated marked prolongation Serum potassium level on the day after hospitalization was 13 mg /100 cc On the second day after hospitalization tracings showed a return to normal the Q T interval measuring 0 4 at a rate of 60 beats/minute T wave was elevated and the base narrowed as compared with the previous tracing Determination of serum potassium level done on this day was *26 2 mg /100 cc*

In another attack six years later serum potassium level was 7 8

(9) Am Hea t J 37 11 6 1134 J 1949

mg and the ECG showed prolonged Q T interval grossly abnormal T waves and depression of RS T segments in all leads Potassium chloride 1 Gm intravenously and 1 Gm orally four times daily was given The following day serum potassium value was 17 2 mg and the ECG appeared normal

In another patient on whom ECG s were obtained during the terminal portion of an attack of familial periodic paralysis U waves were seen in leads I II and CF_4 and T waves were diphasic in lead III

Common to the small number of tracings so far reported in familial periodic paralysis are prolonged conduction times and changes associated with cardiac depolarization and re polarization Prolongation of the P R interval intraventricu lar block and PS T abnormalities occur but with no uni formity from patient to patient The findings which appear most characteristic of hypopotassemia are prolongation of Q T interval depression of RS T segment and low rounded T waves This combination in ECG s is rare

Difficulties in Electrocardiographic Diagnosis of Myo cardial Infarction are discussed by Louis Levy II and Albert L Hyman[1] (Louisiana State Univ) Changes in QRS com plexes indicating infarction are of primary importance in electrocardiographic confirmation of this condition T wave and RS T segment changes alone are not sufficient to indi cate presence of dead cardiac muscle T wave inversion alone may merely reflect a stage of ischemia and RS T segment changes alone may signify a state of injury however unless QRS change appear and persist it is rarely justifiable to make an electrocardiographic interpretation of myocardial in farction Experimental production of myocardial infarction has demonstrated the stages through which cardiac muscle passes and the resultant electrocardiographic sequence of changes which correspond to the stages of ischemia injury and death of muscle The latter causes appearance of perma nent Q waves or QS waves over the area of infarction For Q waves to appear in leads taken over the area of infarction there must be living muscle in the ventricular wall opposite or adjoining the area of infarction since the normal sequence of activation in this area is respon ible for genesis of the Q wave If the infarction involves only the outer portions of the

(1) Am H t J 39 243 6 F b y 1950

enlargement and hypertension Patients selected for study were presumably normal from a cardiac standpoint at all standards except electrocardiographic there were 78 men and 22 women aged 70 and over who were receiving no cardiac medication and who were without significant cardiorespiratory symptoms Auscultation revealed no diastolic murmurs and no systolic murmurs of more than faint or moderate intensity Blood pressure was 160/90 or under A teleroentgenogram showed heart size to be within normal limits No patient gave a history of substernal effort pain or of previous severe chest pain suggestive of coronary occlusion

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(9) Am H t J 37 1126 1134 J 1949

standard electrocardiographic leads I II and III one of two points on the body is connected to each end of the galvano metric string or whatever recording device is used Therefore these leads are called bipolar Leads I II and III represent respectively the difference in potential between the right and left arms right arm and left leg and left arm and left leg Since each standard lead represents the difference in poten tial between two points on the body an ECG will not reveal with certainty the nature and magnitude of the electrical changes occurring at each of these points separately

In order to record electrical potentials of a single point on the body the electrode known as the central terminal T was created by connecting each of the three extremities used for the standard leads to a common point through a resistor of 5 000 ohms The potential of this electrode undergoes no or only slight fluctuation during the cardiac cycle An ECG made by connecting this electrode through a galvanometer with some point on the body is therefore a record of the un complicated potential variations of a particular point In con trast to a standard lead the record is unipolar

Lead IV was then developed It is made by recording the difference in potential between a point on the thorax near the apex of the heart and another on the back close to the angle of the left scapula In a sense this is an asymmetrical bi polar or a relatively unipolar lead in which one electrode being close to the heart contributes potentials of considerably larger size than the more distant electrode In lead IV the problem of determining what is occurring electrically at each electrode is perhaps more difficult than with the standard leads because the electrodes are not equidistant from the source of the potential Furthermore the potential of the distant electrode is not indifferent and varies greatly be tween patients and from time to time in the same patient

It is now generally agreed that the central terminal T is the closest to being a zero potential electrode and with the introduction of a resistance of 500 ohms into each of the three branches the approach to a zero potential is even greater

In 1935 it was demonstrated that the Q wave of leads I II or III in myocardial infarction result because the left arm in lead I and the left leg in lead II were either partial or com

myocardium or is intramural a Q wave may not appear although the QRS configuration is usually modified

Routine ECG s should include the three standard leads and at least precordial leads V_1 through V_6 In patients whose clinical history suggests infarction if these leads are not confirmatory additional exploration with other precordial leads should be undertaken Posterior lesions may show up well in ECG s taken at the ventricular level in the esophagus or in leads taken over the ensiform cartilage Although a large Q wave in lead V_F suggests the possibility of a posterior lesion presence or absence of such a wave can easily be determined from leads II and III Patients without cardiac disease may have a relatively large Q wave in leads III and V_F due to a horizontal clockwise rotated apex forward heart position High lateral lesions are best demonstrated in precordial leads taken over the anterolateral aspects of the third and fourth left intercostal spaces Serial ECG s furnish valuable information Whereas changes in a single ECG may not confirm a diagnosis of infarction serial pictures demonstrating a progression of changes may be diagno tic

The ECG is still only a laboratory procedure which is an adjunct to confirmation of clinical diagnosis of myocardial infarction and should not be relied on completely to establish or disprove diagnosis of coronary occlusion Although in serial ECG s changes of infarction are highly characteristic their absence does not rule out diagnosis of myocardial infarction Too frequently diagnosis of myocardial infarction rests on T wave changes alone and conversely the absence of changes in ECG s is used as the only negative evidence in ruling out diagnosis of coronary occlusion in a patient whose history and other laboratory findings are diagnostic of infarction QRS changes should be present for interpretation by ECG of myocardial infarction however there may be infarction without QRS changes so that confirmation by ECG is impossible Although most patients with myocardial infarction have ECG s which confirm the diagnosis occasionally the ECG shows no characteristic changes in these patients

Unipolar Electrocardiography, Including Intracardiac Leads, in Diagnosis of Myocardial Disease is described by Charles E Kossmann (New York Univ) In taking the

( ) B ll New York A d Med 26 20 46 J a y 1950

tricular hypertrophy and right bundle branch block it is de layed in right precordial leads

As in the standard leads modifications in the precordial leads which occur in cases of ventricular infarction are (1) modifications of QRS (2) elevation or depression of S T seg ment (3) change in T wave Curves are either central or marginal The central curve is characterized by a QRS which is entirely negative and in clinical curves usually slurred or notched The marginal curve is characterized by a QRS which begins with an abnormally deep or broad Q wave followed by an R wave of variable size and occasionally a ter minal S wave The form of the S T segment and T wave with central and marginal curves depends on a variety of factors the most important being age of the infarct

In a considerable percentage of patients found at autopsy to have died from myocardial infarction electrocardiographic abnormalities were not diagnostic Despite newer leads con siderable caution must be exercised before a diagnosis of myo cardial infarction is made on the basis of ECG s alone

Esophageal leads are useful in the study of the electro physiologic behavior of the left atrium because the esophagus is normally in apposition to the posterior wall of this cham ber When the electrode is introduced through the nose it is usually at a level of 32 5-40 cm from the external nares Leads from the atrial region are characterized by a diphasic P wave Leads from the ventricular levels (45 50 cm from the external nares) are used for diagnostic purposes only sporadically be cause the desired information usually can be obtained more easily by leads from the surface of the body Catheterization of the heart has been used to study electrical potentials de veloped in the interior of the heart but it is not likely that this method will have any direct clinical application

Laboratory methods which may soon be of practical value clinically are as follows (1) Plotting null potentials of QRS on the chest by making ECG s from numerous points on the chest and abdomen and determining those in which the algebraic sum of the area of QRS deflection is zero These null potential points are then joined by a continuous line This method though at present unwieldy is useful in studying relative size and direction of Q R and S vectors (2) In vectorcardiography QRS is regarded as a vector which

plete semidirect leads from the region of infarction Later it was shown that the electrical position of the heart could be estimated from relationships between the extremity and pre cordial potentials There has been a tendency to regard the electrical and the anatomic positions of the heart as identical Furthermore it has been assumed that a specific form of QRS in an ECG of an extremity potential means that the extremity has a specific anatomic relationship to a ventricular chamber and/or its cavity It is probable that neither of these assump tions is always fully justified particularly in the abnormal heart

Extremity potentials are often inconveniently small how ever they may be made 50 per cent larger by simply breaking the connection between the central terminal and the extremity being studied

It is possible to approximate extremity potentials by plac ing one electrode on the extremity to be studied and the other on the body at a point as diametrically opposite as possible Curves thus obtained are approximately twice the size of those with the use of the central terminal and no special equipment is necessary

Precordial leads differ from extremity leads principally in that they are closer to the surface of the heart therefore the records more closely resemble direct leads from the sub jacent surface In a normal person the exploring electrode is moved from the right sternal edge (lead V_1) to the left ante rior axillary line (lead V_6) Right precordial leads are char acterized by a small R deep S and T wave which may be in either direction but is usually upright in adults These leads are assumed to be similar to those which would be obtained if the electrode could be placed on the epicardial surface of the right ventricle Left precordial leads are usually character ized by a small Q and S and a prominent R with an upright T wave These leads are assumed to be similar to but smaller than those which would be obtained if the electrode could be placed on the epicardial surface of the underlying left ven tricle Maximal normal time usually given for the interval between beginning of QRS and peak of R wave in leads V_1 and V_2 is 0 03 second and in leads V_5 and V_6 0 05 second In left ventricular hypertrophy and left bundle branch block the deflection is delayed in left precordial leads in h ven

tricular hypertrophy and right bundle branch block it is de layed in right precordial leads

As in the standard leads modifications in the precordial leads which occur in cases of ventricular infarction are (1) modifications of QRS (2) elevation or depression of S T seg ment (3) change in T wave Curves are either central or marginal The central curve is characterized by a QRS which is entirely negative and in clinical curves usually slurred or notched The marginal curve is characterized by a QRS which begins with an abnormally deep or broad Q wave followed by an R wave of variable size and occasionally a ter minal S wave The form of the S T segment and T wave with central and marginal curves depends on a variety of factors the most important being age of the infarct

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Laboratory methods which may soon be of practical value clinically are as follows (1) Plotting null potentials of QRS on the chest by making ECG s from numerous points on the chest and abdomen and determining those in which the algebraic sum of the area of QRS deflection is zero These null potential points are then joined by a continuous line This method though at present unwieldy is useful in studying relative size and direction of Q R and S vectors (2) In vectorcardiography QRS is regarded as a vector which

changes in size and direction from moment to moment and in several planes during electrical excitation of the ventricles The tips of these vectors are joined by a line

Electrokymography of Heart and Great Vessels Principles and Application are discussed by Bert R Boone George F Ellinger and Frederick G Gillick[3] (Nat l Heart Inst Bethesda Md)

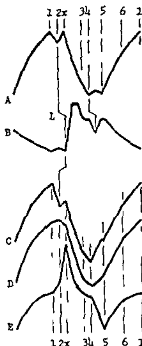
The electrokymograph is an instrument which records movements of the heart and great vessels It is based on the fact that variations occur in transmission of x rays through the heart and/or past its borders as the heart undergoes its phasic volumetric and positional changes It was specifically designed as an attachment for use with the roentgenoscope and electrocardiograph When these three units are utilized together in electrokymography the basic function of each is (1) the roentgenoscope provides the means for observing the cardiovascular silhouette and for positioning the electrokymographic pick up unit over a selected area (2) the electrokymograph converts motions and density changes of the selected points to corresponding current variations and (3) the electrocardiographic galvanometer records these variations on moving bromide paper resulting in an electrokymogram

The electrokymograms of 140 persons aged 17 32 who had no clinical evidence of cardiovascular disease were studied Although no standard positions for the patient or views have been established for routine electrokymographic examination of the heart the following segments of the cardiovascular silhouette are usually examined (1) posteroanterior projection (left ventricle pulmonary artery aortic knob and right atrium) (2) right anterior oblique projection (left ventricle pulmonary artery and dorsally the areas of the right and left atria) (3) left anterior oblique projection (left ventricle left atrium ascending aorta and right ventricle)

The electrokymograph is so connected to the galvanometer that a descending limb results from medial movement of a particular border decrease in density of a part or any combination of these changes which increases transmission of x rays An ascending limb results from lateral movement of a border increase in density or any combination of these changes which decreases transmission of x rays A method

(3) Ann I t Med 31 1030 1056 Dec mbe 1949

of standardizing amplitude has yet to be perfected The left and right ventricular electrokymograms have basically simi lar configurat ons Each cycle consists of a major descending limb essentially due to the medial movement of the ventricu lar border during systole and an ascending limb associated with lat eral movement of the wall in di astole Correlation with a simul taneously recorded carotid sphygmo gram helps to identify onset of ventricular ejection and of isometric relaxation respectively Two lag factors must be taken into account when making the projection from the carotid pulse wave to electro kymogram (1) passage of the carotid pul e wave from the neck through the recording apparatus takes 0 01 second (2) passage of the pulse wave from the root of the aorta to the carotid artery takes 0 01 0 03 second



F g 91 —M thod f nt p t g lect kym g m A C D E v at f l ft t cula l ct kymog m rmal p so B t d phygm g m L cor ect on f to for lag t a t d d g y t m a d p l w t m V t l l d ph f d y l (Cou t f Boon B R t l A I t Med 31 1030 1056 D mb 1949)

Figure 91 illustrates the commonest type of ventricular curve (*A*) with some normal variations (*C* *D* *E*) Using the carotid sphygmogram (*B*) interpretation can be made in terms of the physiologic phases of the cardiac cycle During the iso metric contraction pha e the ventricle is a closed chamber undergoing no volumetric change but is changing from an ellipsoid to a more globular shape producing a positional change of the border Direction of the movement depends on the point at which the record is taken It is usually a descend ing limb in the posteroanterior projection but may be ascend ing or horizontal Usually in the ejection phase (2 3) fol lowing the opening of the semilunar valves at 2 the ven

changes in size and direction from moment to moment and in several planes during electrical excitation of the ventricles The tips of these vectors are joined by a line

Electrokymography of Heart and Great Vessels Principles and Application are discussed by Bert R Boone George F Ellinger and Frederick G Gillick[3] (Nat l Heart Inst Bethesda Md)

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(3) *A I t Med 31 1030 1056 Dec mb 1949*

device and a fluoroscope The photoelectric tube is activated by x rays falling on the fluorescent material and the resulting electric current is led to the electrocardiographic apparatus Variations in intensity of x rays are translated into variations in electric current and recorded as a line on photographic paper marked with lines indicating time intervals An increased flow of current due to increase in intensity of x rays reaching the fluorescent material causes the line being traced on the paper to be directed downward a decrease in current causes the line to be directed upward The pick up unit is mounted between the patient and the fluoroscopic screen and is positioned so that the center of its fluorescent surface is opposite the border of the heart When the heart border moves laterally intensity of the x rays reaching this surface is reduced and the line being traced moves upward To permit identification of the phases of the cardiac cycle on the electrokymogram the carotid pulse is simultaneously recorded on the same photographic paper using a pressure capsule fastened over the carotid artery on the patient s neck

The electrokymographic pattern of various parts of the normal heart shadow is established It is of value in detecting many pathologic conditions By measuring the time relation between onsets of major ascending limbs of the carotid pulse wave and of the pulmonary artery it was found that ejection from the two ventricles does not always occur simultaneously in the so called normal person and that the limits of asynchronous ejection in the normal is ±0 03 second Asynchronous ejection in excess of 0 03 second was almost always accompanied by electrocardiographic evidence of bundle branch block

Although several methods exist for determination of the various arrhythmias it is felt that additional information may be obtained on the mechanics of cardiac motion and thus indirectly the quality of myocardial contraction through study of the arrhythmias Paradoxical motion of an ischemic area of myocardium has been the subject of several articles Such electrokymographic abnormalities were found in patients with no definite electrocardiographic evidence to support a diagnosis of infarction or severe myocardial ischemia

Electrokymographic examination of four of the authors patients with radiologically and surgically proved constrictive pericarditis and calcification produced a constant type of ventricular curve with the appearance of a square wave i e its top is flat and it is practically devoid of secondary waves Similar waves were obtained from localized areas in three

tricular wall moves outward for approximately 0 02 0 03 second The protodiastolic phase (*3 4*) is the interval between the end of systolic ejection and closure of the semilunar valves During the period of isometric relaxation (*4 5*) the ventricles are again closed chambers and no volumetric change occurs Commonly the complex which follows aortic valve down at *4* resembles and is opposite in direction to that of isometric contraction The ventricle fills rapidly in early diastole producing a sharply ascending limb (*5 6*)

Each cycle of the electrokymogram taken from the areas of the atria usually consists of a basic pattern of two or three waves Because the atria are thin walled and relatively inactive chambers riding on vigorously active ventricles transmitted motions from the latter or from adjacent arteries may dominate the curve The effect of this and other physiologic factors may vary from patient to patient on the right and left atrium or on different segments of the same atrium Electrokymograms from the pulmonary artery ascending aorta and aortic knob closely resemble the carotid sphygmogram

The electrokymograph is being used to obtain records of heart density changes hilar shadow movements pulmonary vascular flow etc By placing the aperture of the instrument over the body of the ventricle a record is obtained which resembles the volumetric curve of the ventricle Such a density curve reflects changes occurring with variations in the amount of blood within the heart and alterations in the posteroanterior thickness of the heart muscle Arterial type records were obtained from the hilar shadows and the peripheral lung fields making it possible to study pulmonary circulation However it is impossible to state in what specific types of cardiovascular disease abnormal electrokymographic patterns occur and what clinical value the instrument will have

Clinical Application of Electrokymography The electrokymograph introduced in 1945 by Frederick G Gillick and William F Reynolds[4] (San Francisco) is described as a fluoroscopic microscope designed to detect and record variations in intensity of a small beam of x rays

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(4) Cal fo n a Med 70 407 412 May 1949

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(4) C l fornia Med 70 407-412 May 1949

yond the point of narrowing Less frequently the site of coarctation is seen to be proximal to the origin of the left sub clavian artery a condition loosely referred to as infantile coarctation

Diagnosis of patent ductus arteriosus is best made by physical examination and confirmed by cardiac catheterization Angiocardiography shows elevation and enlargement of the left pulmonary artery and often reveals aortic dilatation at the site of origin of the ductus However this dilatation was observed in two patients who had neither ductus arteriosus nor ligamentum arteriosum and is not invariably present in patients with patent ductus arteriosus

Differential diagnosis of tetralogy of Fallot and transposition of the great blood vessels Eisenmenger s syndrome and common truncus arterio us may be facilitated by angiocardiography In tetralogy of Fallot a left anterior oblique film taken two seconds after beginning injection shows simultaneous opacification of aorta and pulmonary artery simultaneous opacification of a large right and a small left ventricle stenosis in the pulmonary conus or artery and usually a small poorly filled pulmonary arterial tree

Angiocardiography supplies a method for classifying the various causes of dilatation of the pulmonary artery A true lateral view not only reveals the dilatation but rules out presence of pulmonary stenosis a possible cause of dilatation of the pulmonary artery Angiocardiographic demonstration of radiopaque material passing through a septal defect was possible in only about 30 per cent of suspected cases A few notable and convincing exceptions to the contrary were observed but in general diagnosis of septal defect by cardiac catheterization is a far superior method With angiocardiography diagnosis of pulmonary veins draining into the right heart may be made on living patients for the first time surgical implantation of the anomalous vein in the left atrium has been suggested as corrective treatment

Angiocardiography is of value in differentiation of various types of aortic disease It was found that arteriosclerosis does not increase caliber of the aorta Hypertension increases aortic diameter to as much as 46 mm (normal maximum is 38 mm as measured in left anterior oblique) and syphilis causes even greater dilatation Hypertension causes an even

subjects with suspected constrictive pericarditis The roentgen kymograph has also been applied to differential diagnosis of abnormal shadows in the area of the cardiac silhouette The authors approached this problem by setting up a crude model simulating a vessel with an aneurysm and a heart with a spherical tumor adjacent to it Selected patients with known tumors or aneurysms were observed and results were consistent with the electrokymographic patterns found on experimental models

The electrokymograph has certain advantages over the roentgenkymograph Movements as recorded are amplified so that smaller movements are brought out and larger ones more easily studied A larger number of cycles can be recorded Areas to be studied can be selected fluoroscopically in their optimal projections The slit can be alined in the direction of the motion of the part Correlations in time of movements of various parts of an organ are more accurate There are on the other hand some disadvantages Measurement of true amplitude of movements is not yet possible with the electrokymograph The precise point along the border of the part at which movement is recorded is not shown as it is on the roentgenkymogram More co operation from the patient is required The procedure is more time consuming there must be in the fluoroscopic room a technician trained in use of the apparatus but this training can be quickly acquired The authors suggest that the electrokymograph be used much as the spot film is used in gastrointestinal work

Clinical Angiocardiography Critical Analysis of Indications and Findings Charles T Dotter and Israel Steinberg[5] (New York City) made angiocardiographic studies on over 1 000 patients without fatality during 11 years In adequately demonstrating the exact features of coarctation of the aorta angiocardiography is an indispensable preoperative preparation In the left anterior oblique projection the ascending aorta is usually seen to be dilated and to give rise to large brachiocephalic arteries Strikingly dilated internal mammary arteries are often seen paralleling the sternum The actual site of coarctation is usually seen as a narrowing slightly distal to the site of origin of the left subclavian artery Generally the descending aorta is dilated for a short distance just be

(5) A n I t Med 30 1104 11 5 J ne 1949

Five cases were reported and are briefly described here

CASE 1—Girl 11 had systolic murmur pulse of 84 blood pressure of 130/70 axis deviation to left and no other signs of malformation Diodrast® showed a patent ductus arteriosus Operation was not advised because of mildness of symptoms

CASE 2—Boy 10 had left axis deviation and cyanosis Diodrast® revealed tricuspid atresia interventricular communication and hypoplasia of the pulmonary artery Blalock Taussig procedure was advised

CASE 3—Boy 11 had cyanosis enlarged heart left axis deviation and tricuspid atresia Vessels were normally situated but small Operation was not advised

CASE 4—Girl 15 with cyanosis and dyspnea had tetralogy of Fallot Blalock Taussig operation was advised

CASE 5—Boy 17 had Eisenmenger complex and interventricular septal defect Operation was not recommended

Death Following Angiocardiography Charles T Dotter and Frederic S Jackson[7] conducted a survey by questionnaire of all centers in the United States Canada Great Britain and Sweden using angiocardiography A total of 6 824 examinations were reported with death following 26 none later than June 30 1949

Death in three patients was complicated by others factors Twenty one of the other 23 patients had congenital heart disease 17 of these were cyanotic and 5 extremely ill Seventeen deaths occurred in children under 8 all with congenital heart disease 14 of whom were cyanotic No deaths were recorded in persons with healthy hearts except one—a patient with renal arterial disease Three deaths occurred in mongols

The commonest form of death reported was sudden respiratory arrest immediately or shortly after injection of contrast substance Autopsy was done in all but one case but the cause of death was rarely found In about half the cases there was evidence to suggest that the respiratory system was susceptible to injury Pulmonary edema was reported several times

Available data do not indicate that the nature of contrast medium number of injections premedication or general anesthesia significantly influenced angiocardiographic mortality Over half the patients who died received full doses of contrast medium (over 1 cc /kg body weight for children and a total dose of 40 cc or more for adults) and almost all patients were examined in the horizontal position

(7) R d 1 gy 54 5 7 534 Ap 1 1950

dilatation whereas syphilis causes irregularity in the aortic lumen variations in aortic wall thickness and aneurysm In dissecting aneurysm the aortic lumen abruptly narrows and aortic walls thicken at the site of dissection Discrepancy between the size of cardiac chambers and cardiac silhouette in angiocardiography is significant in diagnosis of pericardial effusion Though usually not necessary for diagnosis angiocardiography of patients with pulmonary heart disease shows dilatation of the pulmonary artery and right ventricle and in constrictive pericarditis gross dilatation of the superior vena cava Localization of mediastinal masses also is facilitated by angiocardiography If vessels are stenosed malignancy may be suspected

Angiocardiography in Congenital Cardiopathies Technic and Results in 74 Cases E Donzelot A M Emam Zade R Heim de Balsac J E Escalle and M Antoine[6] (Paris) emphasize the importance of knowledge of the anatomy and physiology of the normal heart and large vessels and correct interpretation of malformations found in treating congenital cardiopathies Opaque visualization is valuable but complicated and not without danger and should be reserved for cases in which other methods fail to give the required information Its special value is in making a correct diagnosis in aiding in the decision for or against operation and in supplying the operating surgeon with information concerning size and course of the implicated vessels

Of 329 patients with congenital heart disease from a blue baby center in Brussels 74 were selected for angiocardiography A total of 408 x rays were taken of which 35 were failures 77 fair 187 good and 109 excellent

Technic—Children were hospitalized and tested for allergy renal function and circulation time During the test they were recumbent and x rays were made in the anteroposterior projection Injection of 1 cc /kg body weight of 70 per cent diodrast® solution was made into the external jugular vein with a small trocar inserted without local anesthesia The trocar fitted to a tube with Y connection One arm of the Y led to a container of salt solution with a drop dispenser the other arm to the syringe containing diodrast® X rays were taken before injection and after use of diodrast® at a rate of six exposures in five to six seconds Patients reactions were feelings of warmth Elimination of diodrast® amounted to 70 per cent at the first urination

(6) A h d mal d coe 4 35 49 Ja ry 1949

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(7) R d l gy 54 527 534 Ap 1 19 0

New technics for study of this group of disorders continue to be developed and of them the isotopic method would seem to offer special promise for the future In most instances the simple clinical methods are adequate for arriving at an accurate diagnosis A number of new vaso dilator drugs are being used and definitive knowledge concerning their value as compared to each other and to such surgical procedures as sym pathectomy should soon be forthcoming —Ed

Certain Aspects of Nature and Treatment of Oligemic Shock are discussed by Irvine H Page[8] (Cleveland Clinic) One fact on which all investigators of shock are agreed is that shock represents all embracing dissolution Therefore its over all effects can probably best be measured by a quotient repre senting cardiac output and oxygen consumption as a measure of effective blood flow In Page s opinion Gesell has most nearly approached this concept with his nutrient flow He assumes that in shock transport of nutrient material and carrying away of waste are interfered with either by dilution of blood or by reduction of flow Since effective blood flow is seriously reduced for long periods it is not surprising that widespread damage occurs Whether the lack of one specific element such as oxygen is chiefly at fault or whether many substances are involved is not known For reasons such as these it is probably unwise to continue exclusive use of the terms anoxia or hypoxia to explain the cause of tissue changes Whatever the mechanism widespread tissue ischemia of suffi cient persistence results in shock Blood pressure may be ex cessively low but so long as no tissue ischemia occurs shock does not appear

It has taken possibly 30 years to recognize fully the im portance of oligemia as a cause of shock Of especial impor tance have been demonstrations that loss of plasma at site of injury often is sufficient to cause shock Most investigators would now agree that this is not the only factor in production of shock but is certainly of prime importance Another vital demonstration was that in shock cardiac output is low These facts with low blood pressure produce the picture of early shock Then begins the period of generalized dissolution in which so many chemical reaction paths are disturbed as to

(8) Am Heart J 38 161 191 August 1949

cause the investigator to become both baffled and frustrated

In an attempt to find a standard method for production of experimental oligemic shock Page has studied the shock procedure in 482 dogs in the past three years Despite standardized technics survival was so profoundly influenced by unknown factors entirely beyond control that establishing a regularly reproducible standardized shock seems to be only statistically possible

The problem of vasoconstriction in shock viewed superficially seems relatively simple But closer analysis reveals extraordinary complexity and despite much good work there *is still no satisfying answer There seems to be little disagree*ment that vessels of the limbs are constricted and there is little doubt that resistance to blood flow is increased in liver and spleen The only important area so far studied in which resistance decreases rather than increases is the coronary circulation Vasodilatation appears to play a prominent part in decrease in resistance in coronary flow Vasoconstriction in the kidney is of special interest since this organ receives almost one fourth of total cardiac output Renal blood flow decreases sharply after hemorrhage with a disproportionate decrease in glomerular filtration Repeated prolonged hemorrhage decreases ability of the kidneys to respond to transfusion by restoration of control blood flow and filtration rate Explanation of this vasoconstriction so intense early and persistent seems to be partly humoral and partly nervous

As far as the mechanism of vasoconstriction is concerned there is no cogent evidence to suggest the primacy of failure of the vasomotor center At least three possibilities suggest themselves to explain why blood vessels constrict when blood volume is reduced physical factors active neurogenic constriction and active humoral contraction Presence of humoral factors has been established but function of this renal vasopressor system renin reninsubstrate and angiotonin in shock is not clear Although it is inferred that the renin vasopressor system acts as a homeostatic mechanism there is no proof of this There is still another humoral vasoconstrictor possibility It has long been known that defibrinated blood or serum does not perfuse well through isolated organs because of the vasoconstriction it causes In conjunction with others Page has isolated from serum a purified substance named serotonin

with vasoconstrictor activity more than twice that of an equal weight of epinephrine As yet nothing is known about the *part if any played by serotonin in shock*

Page has found no regular correlation between survival after shock procedure and a number of obvious environmental factors such as weight of the animal amount of blood required to lower blood pressure degree of hydration season initial hemoglobin or hematocrit value and initial blood pressure Since there is good evidence to suggest that as shock progresses efficiency of the myocardium becomes impaired effect of ouabain on survival was studied It did not alter survival but tetraethylammonium chloride which blocks ganglionic transmission in all autonomic ganglions increased survival significantly Increased survival appears related to the fact that in dogs with total sympathectomy blood pressure can be reduced to lower levels and for longer times without producing shock than can be done in normal dogs Difference in reaction can be correlated with peripheral blood flow

In treatment of shock all agree that blood volume must be restored to normal in as short a time as possible In the terminal phase every minute counts Among the reasons for giving blood by artery instead of by vein are the following Blood pressure is restored to normal levels within a few minutes and pressure is controllable Blood volume deficits are automatically corrected That amount of blood will be taken into the circulation which is required to fill it at a given arterial pressure When heart and respiration have failed blood given into an artery often brings about resuscitation The procedure is simple the apparatus is mobile and nothing that is not ordinary hospital equipment need be used Given by artery little more than half the amount of blood required when blood is given by vein is needed to restore arterial pressure In emergencies it makes little difference what fluid is administered to keep the circulation going until the more suitable blood is available

Arterectomy in Treatment of Intractable Pain Following Recovery from Acute Arterial Occlusion N E Freeman F H Leeds and R E Gardner[9] (Univ of California) report 10 cases of acute occlusion of a major artery by thrombosis or embolism in which the extremity was viable but intract

(9) Am H t J 38 3 9 335 Septembe 1949

able diffuse pain and distal hypoesthesia with a protopathic pain response subsequently developed. The pain was continuous and subject to severe spontaneous exacerbations This pain had been termed ischemic neuritis Some patients found relief in grasping the foot and gently rocking back and forth in bed dependency did not seem to help the pain Walking appeared to ease it but most patients stated that exercise was prevented by intermittent claudication All complained of numbness in the involved member The pain was relieved temporarily by lumbar sympathetic block. The site of obstruction was visualized by arteriography All but one patient underwent operative removal of the thromboed segment After operation the severe spontaneous pain was relieved though other types of pain due to ischemia might persist Two patients died of acute coronary occlusion nine days and four months respectively after surgery neither had had recurrence of pain up to the time of death The patient in whom arterectomy was not done was treated with rest and vasodilators for two years there was no change in the character of the pain over this period

None of the patients showed any objective improvement in peripheral blood flow although functional recovery in the postoperative period would suggest some improvement in the circulation Eight patients showed no increase in ability to walk but in two there was some improvement over a period of months The neurologic findings remained unchanged

Arterectomy is a relatively minor procedure and can be done even in the poor risk patient All operations were performed under local anesthesia Usually only 2 3 cm of the thrombosed vessel was excised. The authors believe that the relief of pain is not the result of any improvement in circulation but rather is due to interruption of some nerve reflex from the region of the thrombosed artery

***Radioactive Isotopes in Study of Peripheral Vascular Disease* Further Studies on Circulation Index with Evaluation of Diagnostic and Therapeutic Value of Priscoline** * The condition of the peripheral vascular circulation can be estimated by radioactive isotopes A method using radioactive phosphorus (P^{32}) to test the status of the peripheral circulation has been described previously Data so obtained not only afford a survey of circulatory efficiency but can be helpful as a guide to prognosis and treatment The method is applicable

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None of the patients showed any objective improvement in peripheral blood flow although functional recovery in the postoperative period would suggest some improvement in the circulation Eight patients showed no increase in ability to walk but in two there was some improvement over a period of months The neurologic findings remained unchanged

Arterectomy is a relatively minor procedure and can be done even in the poor risk patient All operations were performed under local anesthesia Usually only 2 3 cm of the thrombosed vessel was excised The authors believe that the relief of pain is not the result of any improvement in circulation but rather is due to interruption of some nerve reflex from the region of the thrombosed artery

Radioactive Isotopes in Study of Peripheral Vascular Disease Further Studies on Circulation Index with Evaluation of Diagnostic and Therapeutic Value of Priscoline * The condition of the peripheral vascular circulation can be estimated by radioactive isotopes A method using radioactive phosphorus (P^{3}) to test the status of the peripheral circulation has been described previously Data so obtained not only afford a survey of circulatory efficiency but can be helpful as a guide to prognosis and treatment The method is applicable

to investigation of new drugs designed to treat peripheral vascular disease Morris T Friedell Walter Indeck and Fenton Schaffner[1] (Chicago) report observations on the use of priscoline® whose effect occurs chiefly at the termination of sympathetic nerves in vascular smooth muscle

The circulatory index is determined by intravenous injection of 200 μc (P^{32}) as a phosphate ion and application of a thin walled beta counter to the sole Counts per minute determined with a scaling unit are plotted semilogarithmically with time as the logarithmic function Values ordinarily fall in a straight line the reciprocal of the slope of this line is designated the circulatory index The most useful part of study of the peripheral vascular circulation with isotopes is alteration of the circulatory index by one of the vasodilators

Four main types of responses of the circulatory index have been noted In group 1 the circulatory index is initially in the arteriosclerotic range (below 0 110) and rises to normal after therapy In group 2 it is low and falls to a lower level after treatment In group 3 the index seems to be subject to variation This group is therefore divided into subgroup 3a in which the initial index is above 0 110 and falls to the arteriosclerotic range after treatment and subgroup 3b in which initial index is above 0 110 but below the mean of the normal group and rises beyond the normal range after treatment In group 4 the index is above normal range and rises even higher after treatment

Classifications by these groups have been correlated with clinical findings in 82 patients Correlation of clinical (subjective and objective) response to a drug with the type of alteration obtained in the circulatory index revealed that groups 1 and 2 patients yield the best clinical responses Group 3a patients do better than group 3b treatment was ineffective for group 4 patients

Intravenous injections of priscoline® have been used in recent months to determine these groupings In addition oral medication with this drug over prolonged periods has been used for therapy of various peripheral vascular disorders Prognosis of the groups as determined with priscoline® coincides with that of groups determined by other vasodilating mechanisms The drug appears safe and only occasional un

(1) Arch Int Med 85 667 674 Apr 1950

pleasant side reactions were encountered Priscoline® is apparently more effective in conditions in which symptoms are due primarily to diminished blood supply It is less effective in severe associated causalgic states

Measurement of Regional Circulation by Local Clearance of Radioactive Sodium Dynamics of the blood tissue exchange of a diffusible inert substance has recently assumed significance as a basis for measurement of blood flow If the diffusible tracer substance instead of being administered in the general circulation is introduced into the tissue in question it is apparent that its clearance from the tissue will depend on and possibly be a measure of local tissue circulation Seymour S Kety (Univ of Pennsylvania) made a mathematical analysis of the clearance of such an injected substance

According to this analysis the tissue deposit of diffusible tracer (Na^{+}) should decrease along a single exponential curve which if plotted semilogarithmically should yield a straight line whose slope (clearance constant) is a quantitative measure of total ability of the local circulation to remove and to supply freely diffusible substances

For testing applicability of the theory the human gastrocnemius muscle was chosen In all cases in which nothing was done to alter circulation clearance followed a simple exponential curve indicating the validity of the theoretical derivation To test responses of the clearance constant to alterations in circulation studies were done in which a control period was followed by some procedure designed to speed or slow local circulation Application of a tight tourniquet above the knee was invariably and immediately followed by sharp reduction in clearance constant to practically zero Release of the tourniquet after 10 minutes was associated with a clearance more than twice normal undoubtedly a reflection of reactive hyperemia Exercise of the gastrocnemius for one minute caused a considerable increase in clearance rate

Kety suggests that the clearance constant represents a valid and convenient measure of local circulation in its broadest sense and is therefore a clinically useful determination

Differential Diagnosis of Peripheral Vascular Diseases is outlined by Walter Redisch[3] (New York City) In the scalenus

(2) Am H t J 38 321 328 S pt mbe 1949
(3) J M Soc N w J y 46 38 243 M y 1949

anticus syndrome x ray verifies or excludes cervical rib or related anomalies of the transverse process Enucleation of a cervical disk may produce pain resembling that of scalenus anticus syndrome but is not accompanied by vascular symptoms Post traumatic segmental arterial spasm starts suddenly and is relieved by nerve block or etamon® chloride Sudeck s atrophy is diagnosed by x ray Primary Raynaud disease starts in the upper extremities occurs predominantly in women and invariably leads to trophic changes Occupational peripheral vascular diseases in workers with pneumatic tools pianists and typists may show a secondary Raynaud phenomenon In erythromelalgia (Weir Mitchell s disease) extremities are warm and painful Distress and pain is brought about by heat and relieved by cold whereas the contrary as a rule is true for occlusive disorders

Periarteritis nodosa involves peripheral arteries in regular rosary like beading biopsy is valuable though diagnosis will usually be suggested by other features of the disease Primary acute arteritis is rare and is seen mostly in children Secondary arteritis is not so rare and may occur in all age groups Longlasting deep venous disease almost invariably leads to secondary arterial disease Pallor absence of pulsations and trophic changes suggest that the process has extended from the vein to the artery Superficial thrombophlebitis in a varicose vein is easily palpated as a hard nodule or cord with or without surrounding inflammation Pain on pressure may be present in neuritis to the same extent as in deep thrombophlebitis Homans sign however is absent in neuritis and present in a high proportion of cases of deep thrombophlebitis Absence of diminished reflexes presence of edema peripheral arterial disease or cardiovascular disease cachexia and history of prolonged bed rest preceding operation or childbirth all favor deep venous disease Pulmonary embolism is of course a handicap in diagnosis

Arteriovenous fistulas must be differentiated from hemangiomas and pulsating metastases In hemangioma as in arteriovenous fistula there is a localized protruding convolute of dilated veins but in contrast to the fistula no thrill or bruit and a Nicoladoni Branham sign of bradycardia cannot be elicited Pulsating metastases are almost invariably pathognomonic of primary cancer of the thyroid Thrill and bruit are

frequently present A predilection site is over the hip bone the mass appearing under skin of the buttocks Lymphangiomas may occur alone or mixed with hemangioma They are benign but may be extensive and affect a whole arm Differentiation of telangiectasias of the skin is easy Simple arborizing and spider telangiectasias are frequent in liver cirrhosis and in women during pregnancy and are occasionally seen in healthy persons Harmless papular capillary telangiectasias are easily differentiated by means of their red and firm surface from the livid more flabby lesions of Rendu Osler disease (familial hemorrhagic telangiectasia) The former never bleed the latter are characterized by a tendency to profuse bleeding Harmless papular telangiectasias occur almost invariably after middle age Port wine lesions of capillary nevus flammeus the vascular birth mark are well known

Glomera are physiologic structures present in large numbers in fingers and toes and in smaller numbers el ewhere in the skin which aid the heat regulation of the body Occasionally one or several glomera may produce a new growth and become visible as a small nodule in the skin Their differentiation from small hemangiomas is easy because of the extreme painfulness of the glomus tumor Osler s nodes are not present in an otherwise healthy person and the hemangioma is not characterized by the purplish blue color of a glomus tumor

The obliterating endarteritides frequently are accompanied by such generalized signs and symptoms as hypertension in lead poisoning and eye lesions in ergot poisoning Syphilitic and tuberculous types of endarteritis u ually exhibit some other manifestations of their respective etiologies Differentiation of thromboangiitis obliterans from obliterating arteriosclerosis may be difficult Manifestations of arteriosclerosis in other parts of the body and presence of diabetes suggest obliterating arteriosclerosis rather than Buerger s disease There may be a history of heavy tobacco smoking in both disorders this is invariably found in Buerger s disease Buerger s disease usually starts in the lower but frequently affects upper extremities Obliterating arteriosclerosis on the other hand is usually confined to lower extremities Angiography is valuable in differentiating Buerger s disease from obliterating arteriosclerosis the typical segmented interruption of arterial filling with enormous collateral circulation in the small vessels in the

former is an impressive contrast to the localized block with or without opening of new channels in the latter

Usually arterial thrombosis occurs in persons who have generalized peripheral vascular disease especially arteriosclerosis and is characterized by sudden onset pain and pallor with or without cyanosis In pure venous thrombosis signs of arterial occlusion disappear after five or six hours If they persist more than six hours and are not influenced by measures known to release arterial spasm then it must be assumed that there is an associated organic arterial lesion

Chilblains are spots of swollen slightly cyanotic erythema caused by cold injury of minute blood vessels they occur in children and young adults mostly female Chronic perniosis has logically the earmarks of chronic local disturbance in minute blood vessels Ulcerations are frequent but superficial Chronic perniosis is localized chiefly around the ankles the predilection site for varicose ulcers is the shin Frostbite and trench (immersion) foot are thrombotic diseases of arterioles venules small arteries and sometimes small veins

Diagnosis of Portal Vein Obstruction Studies of Intestinal Absorption of Glucose Using Abdominal Collateral Veins In portal venous obstruction the collateral circulation carries part or all of the blood ordinarily consigned to the portal vein The collateral veins therefore may be expected to transport the products of intestinal absorption circuitously around the obstruction F Tremaine Billings Jr and Harold E DePree[4] (Nashville Tenn) attempted to determine whether the products of intestinal absorption could be demonstrated in the collateral veins of the abdominal wall in patients with portal vein obstruction and if so whether such a procedure might not assist in differential diagnosis of the etiology of ascites The oral glucose tolerance test was used Blood was drawn at regular intervals after ingestion of glucose simultaneously from the antecubital vein and from a vein in the abdominal wall and the blood sugar content was measured Sixteen patients with ascites were studied and 2 without ascites were controls

With hypertension of the portal vein higher levels of sugar were often demonstrated in blood from the veins of the abdominal wall than in blood from the antecubital vein The

(4) B ll J hn H tk H p 85 183 199 Sept mbe 1949

authors suggest that this procedure is helpful in determining whether or not there is portal vein obstruction

Arterial Air Embolism is discussed by Thomas M Durant M J Oppenheimer M K Webster and Joan Long[5] (Temple Univ) Air embolism may be classified into two types depending on site of entrance of air into the body *In the first* type air enters a systemic vein and tends if present in sufficient quantity to cause obstruction of the right ventricular outflow Up to 100 150 cc or more of air may be necessary to produce death This type has been called pulmonary air embolism since the pulmonary circulation is involved Air which *enters the pulmonary veins produces an entirely different clinical picture* and causes arterial air embolism The serious manifestations produced are dependent on obstruction of systemic arteries especially of the central nervous system and coronary vessels

It was formerly believed that air responsible for arterial air embolism either was injected from a pneumothorax apparatus or in the case of thoracic surgery was aspirated into open pulmonary veins However embolisms have occurred frequently in pneumothorax work when no air has been injected Others have occurred which complicated the tapping of pleural effusions for which no extrinsic air source could be implicated It is now known that air already present in the thoracic cavity can be an important source of embolisms if the therapeutic procedure provides access of air to the venous system and the pressure gradient from source to vein is sufficient Sources of air in arterial air embolism may be classified as intrinsic air in alveoli pulmonary cavities or pleural cavity extrinsic air either injected aspirated from tubing of *pneumothorax apparatus or aspirated into pulmonary veins* during open chest procedures In pneumothorax work injected air may reach a pulmonary vein directly but air may also reach such a vein indirectly if pressure in the pneumothorax cavity is raised sufficiently to tear an adhesion with production of a pleurovenous fistula Air from intrinsic sources cannot reach pulmonary veins unless trauma of the thoracic procedure produces an opening from source to vein There must also be a sufficient pressure gradient from source to vein and some factor to maintain patency of the opening

(5) Am H t J 38 481 500 O tob 1949

The necessity for such a chain of circumstances explains the rarity of accidents when needles are introduced into normal lung tissue After air from either an extrinsic or an intrinsic source has entered the pulmonary vein it is carried to the left heart and into the aorta From this point its route is determined to a considerable extent by the patient s position Air buoyancy tends to cause the gas to enter those branches of the aorta which are superiorly oriented with relation to the trunk of the vessel When air has reached the terminal arterial branches of an organ the effects produced are the result not only of the mechanical obstruction of the smaller vessels but of a neurovascular mechanism producing vasoconstriction

Clinical manifestations of arterial air embolism are somewhat varied They may be of sudden onset or there may be warning symptoms such as dizziness or faintness just before severe features become manifest After the warning symptoms there is usually loss of consciousness of variable duration Convulsions occur in less than half the cases After return of consciousness various localized neurologic signs may be noted These may disappear within a few hours or may persist for months Generalized cyanosis is noted in most instances and respiratory disturbances most often slowing of the respiratory rate are usually present Manifestations of peripheral vascular collapse are frequent These clinical features are nonspecific but there are five features which may be regarded as pathognomonic (1) detection of air in retinal vessels by ophthalmoscopic examination (2) Liebermeister s sign—occurrence of sharply defined areas of pallor in the tongue (3) marbling of skin (4) air bleeding—presence of air bubbles in blood escaping from a small skin incision in the most superior portion of the body and (5) x ray evidence of air in cerebral vessels The diagnostic value of these features is so great that they should be searched for in every case in which there is a possibility of arterial air embolism

The frequent involvement of the coronary arteries in arterial air embolism has been demonstrated by experimental and postmortem studies and it has been stated that obstruction of coronary arteries must be considered important in all cases of air embolism originating in the pulmonary circulation However there is a lack of data on whether air introduced experimentally into the coronary circulation can pro

duce ischemic areas in the myocardium or electrocardiographic changes of infarction The authors therefore carried out 18 experiments using 16 dogs In 14 experiments air was injected into the anterior descending branch of the left coronary artery and in 4 into either the left auricle or the pulmonary vein

On the basis of results it can be stated that air is not well tolerated within the dog s coronary circulation because six animals died and ischemic areas were induced within the myo cardium in all dogs Electrocardiographic changes were iden tical with those observed in instances of ischemia induced by other means The effects of vascular obstruction may be tran sient the air being rapidly disposed of but in some instances they may be sufficiently prolonged to result in persistent ischemia of the myocardium even after air bubbles can no longer be detected with the lumen of the vessel involved

The importance of the principle of air buoyancy was dem onstrated in these experiments in that air filled the superiorly located portions of the coronary circulation The importance of the application of this principle by use of the head down position in prevention of cerebral air embolism has been dem onstrated by others It seems logical to assume that the same principle could be applied effectively to prevention of coro nary involvement Since in man the right coronary artery arises anteriorly from the right aortic sinus and the left coro nary artery arises mesially from the left posterior aortic sinus it should be possible to prevent air from entering these vessels by placing the patient in a position midway between left lat eral and prone There is indication that the initial dose of air may not be the only one since a fistula between the pulmonary vein and a pneumothorax or other air containing cavity may be opened and closed repeatedly Hence if there are warning symptoms of air embolism and the initial dose is not fatal it would appear logical to place the patient immediately in the favorable position described so that any subsequent emboliza tion may not have serious effects To prevent cerebral embo lism the patient should also be placed with head down It would seem wise to maintain such a position for several hours to allow the fistulous tract to heal

Pathophysiology and Treatment of Lower Leg Stasis Syn drome are outlined by Gunnar Bauer[6] (Gen l Hosp Marie

(6) A g logy 1 1 8 F bru ry 1950

stad Sweden) At this hospital division and resection of the popliteal vein has for some years been the main therapeutic procedure in all patients with a lower leg syndrome of chronic edema induration ulceration and pain

Man s erect position is known to cause a certain amount of venous overloading in the lower parts of the leg In healthy persons this superfluous blood is easily removed by contractions of the calf muscles which act as a peripheral heart This mechanism demands normal functioning of the valves in the femoral and popliteal veins In patients with lower leg edema induration ulceration and bursting pain it has been demonstrated that these large veins are incompetent their valves having been destroyed by thrombosis or by phlebosclerotic processes In such cases superfluous blood cannot be effectively removed by contraction of calf muscles every relaxation of these muscles being immediately followed by a back flow of blood down the valveless main trunk This results in permanent venous stasis eventually followed by pain and tissue changes

A remedy for this condition is blocking of the main trunk in the popliteal region After this operation the calf muscle contractions drive the blood through numerous fine calibered channels into the muscle veins of the thigh and no backflow occurs Considerable experience with phlebography demonstrated the extraordinary ease with which collateral venous channels form the instant main trunks are blocked Study of the lower extremity in the vertical position after popliteal blocking showed that after a few calf muscle contractions the deep vein trunks were nearly empty and all blood was being driven through numerous channels past the level of the knee up into a rich network of mainly muscle veins in the thigh Once in the thigh blood was amply taken care of by the lively circulation in the powerful muscle masses in that part of the leg

Popliteal vein division has been performed 194 times at the Mariestad hospital The operation was apparently entirely risk free and immediate results were good Though the observation period is too short to allow final evaluation of late results follow up examination of 80 patients after 1 2½ years is encouraging

Nonsurgical Treatment of Peripheral Vascular Disorders is discussed by Walter Redisch[7] (New York City) General therapy of peripheral vascular disorders is concerned first with prevention of circulatory insufficiency second with promotion of increase of circulation and third with maintenance of compensation of insufficient circulation if compensation is achieved Requiring management of chronic arterial insufficiency are all patients with signs of peripheral arterial insufficiency or presenting evidence sufficient to suggest that they may be threatened by this disorder in the future The peripheral vascular routine includes prohibition of tobacco and food or drink containing rye grains prescription of 2 or 3 oz Scotch or Bourbon whiskey daily or 3 glasses of wine a foot care program scrupulous care to avoid injuries to extremities avoidance of exposure to cold and therapeutic appliance of postural changes This routine is the baseline for any additional active special treatment Management of chronic venous insufficiency on the other hand is aimed at facilitating venous deflux Sleeping with the foot of the bed elevated wearing of elastic bandages or stockings and walking exercises with these stockings in place is the basis

Papaverine hydrochloride about 0 05 Gm by intra arterial injection effects release of arterial spasm This heroic treatment has its place in acute arterial occlusion of all kinds including pulmonary embolism Oral doses of 50-100 mg three times daily are justified in vasospastic disorders and definitely beneficial in so called vascular crises Theobromine derivatives including aminophylline are worthless Nitroglycerin seems to be effective in the visceral circulation only Effects of histamine are probably confined to the skin Ether intravenously is an effective vasodilator but the danger of hemorrhage is too great Results with acetylmethylcholine chloride are not impressive and effects of intravenous use of typhoid vaccine are transient and do not justify use of so incapacitating a method in spastic disorders Priscoline ® an imidazolene derivative has some usefulness in Buerger s disease (50 mg three times daily) There is no question about the beneficial effects of intravenous use of procaine on arterial spasm The most powerful and reliable vasodilators however are the different alcohols The simplest and one of the most efficient

(7) J M 1 Soc N w Jersey 46 363 375 A g 1949

is still ethyl alcohol in the form of good whiskey or brandy Nicotinic acid produces vasodilatation only in cutaneous vessels Niacinamide does not cause vasodilatation Nicotinic alcohol seems to hold good promise as a vasodilator

Treatment of primary Raynaud s disease is surgical Secondary Raynaud s phenomenon calls for treatment of any underlying vascular disease and usually treatment of the underlying psychoneurosis Wier Mitchell s disease (erythromelalgia) is one of the conditions in which for unknown reasons salicylates are almost a specific for pain In obliterating endarteritis in addition to rigid vascular routine therapy depends on etiology Treatment of Buerger s disease is predominantly based on the vascular routine as is treatment of obliterating arteriosclerosis Dietary treatment of arteriosclerosis is important and diet should always be low in fat and cholesterol

Management of acute arterial occlusion consists of intravenous or intra arterial use of papaverine intravenous use of procaine or diethylaminoethanol keeping the limb warm and watching for results for three to six hours If preliminary results are favorable vasodilators are continued if unfavorable paravertebral nerve block is done Whenever the patient s state permits Redisch proceeds with sympathectomy if nerve block gives a favorable result Treatment of arterial occlusion with anticoagulants is still experimental If the cause of the occlusion is an embolus in an otherwise not diseased blood vessel embolectomy should be performed Thrombectomy with resection of the diseased part of the blood vessel has no indication

In acute thrombophlebitis and prevention of thrombo embolism in addition to elevation and rest there are but three basic approaches use of anticoagulants surgical ligation of efferent veins and the combination of both When thrombophlebitis is diagnosed before pulmonary embolism it seems unnecessary to proceed with venous ligation unless anticoagulant therapy is contraindicated It is contraindicated in all conditions in which there is an abnormal tendency to bleeding In these patients early ligation of veins on both sides is the procedure of choice Patients with early diagnosis of non extensive *thrombophlebitis in whom no contraindication* to anticoagulant therapy exists must be treated with this method

Chemical Sympathectomy H A Haxton[8] (Manchester) reports his experiences with phenol injection of the lumbar sympathetic ganglion in patients with various conditions

TECHNIC.—Two 12 cm needles are inserted through skin wheals 7 cm from the midline and opposite the second and third lumbar vertebrae The needle must establish contact with the side of the vertebral body and by manipulation it is persuaded to slide tangential to the bone for a further distance of 1 2 cm. The point may be felt to pierce the psoas fascia and when it is in the correct plane a tentative injection of procaine should flow easily A careful watch must be kept for the welling of blood or cerebrospinal fluid from the needle Preliminary injection of 2 ml of 4 per cent procaine is made As a rule the patient notices warmth in the limb before it is detected by the ob erver but the sole of the foot should begin to warm up a few minute after injection unless there is severe organic arterial obstruction Provided there are no symptoms of numbness or paralysis the injection is completed with a total of 10 12 ml of 10 per cent phenol in water The patient remains in the lateral posi tion 15 minutes to prevent spread of the injection and can then get up and go home if ambulant.

In over 90 per cent of cases a warm dry foot resulted and in 60 per cent the foot remained warm and dry for months For some patients in whom the effect did not persist the injec tion was repeated and a good and lasting result obtained The longest follow up was nearly two years and the signs of sympathetic denervation remain Complications were few and consisted mainly of some irritation of the genitofemoral nerve which developed in about 10 per cent of patients caus ing hyperesthesia in the groin In one patient a low spinal analgesia lasted three hours and weakness of the quadriceps on the injected side lasted three months it was thought that the needle was incorrectly placed and the injection must have entered an intervertebral foramen

Uniform success was achieved by chemical sympathetic injection in six patients with intractable pain in amputation stumps In another patient with hyperhidrosis of the feet there was immediate and dramatic cure which remained complete Six patients with cold blue legs painful nodules of fat necrosis and in some chronic ulceration were treated with lasting benefit in all but one Similar relief was provided in two pa tients with severe chilblains In 65 patients with arterioscle rotic legs profound and lasting relief from rest pain was achieved in half and considerable relief in nearly all the re

(8) B M J 1 10 6 10 7 J 11 1949

mainder Pain due to inflammation near a gangrenous or infected part was not however relieved by this treatment or by sympathectomy Phenol injections greatly improved the precarious circulation in the foot and in several patients with gangrene of one toe healing was achieved with loss of only the affected digit Patches of gangrene on the heel and chronic ulcers on the outside of the leg have likewise healed with preservation of the limb The majority of 23 patients treated for intermittent claudication stated that they were benefited some considerably Of 58 patients with old white leg and similar deep venous thrombosis treated by phenol injection all but a few were benefited Explanation of this improvement lies partly in the removal of venous spasm with a resulting fall in venous pressure and partly in the improved nutrition of the capillary walls with reduced transudation into the tissues

Experiences with Tetraethylammonium Bromide, an autonomic blocking agent are described by Gunnar Biorck and Borje Ejrup[9] (Stockholm) The effect of intravenous and intramuscular injections of a solution of the compound were *studied by means of blood pressure recording electrocardio*grams oscillograms (at rest and after exercise) skin temperature determinations electrocardiographic hypoxemia tests and determination of oxygen consumption

Results revealed that intravenous injection of tetraethylammonium bromide in man is followed by an immediate short lasting fall in blood pressure and in increased heart rate The effects were greater in hypertensive patients than in normal persons rate of injection and dosage were important In rabbits effect of intravenous injections of tetraethylammonium bromide on blood pressure was depressor whereas in cats it was depressor only with small and moderate doses and pressor with larger doses In all instances heart rate was slowed These findings can be attributed to blocking of transmission of tonic impulses in the autonomic nervous system

Injection of tetraethylammonium bromide was almost immediately followed by increased skin temperature both in normal persons and though to a lesser extent in patients *with* occlusive changes in arteries This increased skin temperature was independent of the fall in blood pressure Although oxy

(9) A ta med Scand 133 299 320 1949

gen consumption generally increased during injection no certain increase in oxygen consumption was found during the period of maximal rise in skin temperature No definite improvement of the electrocardiogram after induced anoxemia in cases with coronary insufficiency (the hypoxemia test) was observed neither shortly after injection nor after a series of therapeutic injections

Oscillograms on patients with occlusive changes in arteries given tetraethylammonium bromide did not demonstrate any improvement immediately after injection although the patients were subjectively improved Fifteen of 20 patients with occlusive changes in arteries showed after a series of 20 injections of tetraethylammonium bromide both subjective and objective improvement as measured by amount of exercise performed and by more rapid oscillographic recovery period Effect depended on completeness of the block In many large persons 5 ml of the drug was insufficient for production of complete block The larger doses (8 or 10 ml) required proved safe when given slowly The authors recommend a dose of 0 10 Gm /kg body weight There were few complications to administration of tetraethylammonium bromide The *drug is not recommended for use in patients with complete* heart block as lack of a cardiac mechanism compensating for the sudden drop in blood pressure may cause cerebral anemia and shock

Etiology of Gravitational Ulcers of Leg The term gravitational ulcer refers to chronic ulcers which occur on the lower half of the leg from chronic venous stasis of the lower limb Such ulcers are associated with one or more of the following signs of chronic impairment of venous drainage edema cyanosis induration sclerosis pigmentation loss of hair eczema and varicose veins of the affected limb Although these ulcers have long been thought to be due to varicose veins clinical observation and careful dissection have shown that many are due to obstruction of deep or superficial trunk veins

S T Anning[1] (Univ of Leeds) investigated the cause of ulceration in 270 patients by clinical examination and in a few cases by phlebography There was 192 women and 78 men in this series

In 88 6 per cent venous stasis was due to previous throm

(1) B t M J 2 458 464 A g 27 1949

bosis of deep veins in the leg Thrombosis followed pregnancy in 69 women *the first ulcers occurring 3 months to 27 years* after a postpartum white leg Antepartum thrombosis though less common than postpartum phlebitis is well recognized as a complication of pregnancy Fifteen patients gave a history of sudden pain and swelling of one or both legs during pregnancy Edema of the affected legs persisted and some patients developed varicose veins for the first time Thrombosis of the deep veins of the leg had probably occurred

Injury to one or both legs without fracture occurred in *60 patients Of those in whom there was no evidence of* chronic venous insufficiency before injury 23 gave a history of swelling of the leg and 10 developed varicose veins after injury thrombosis from the injury was the probable cause *Injury to the leg with fracture* occurred in *11* patients *Both* direct injury to a vein and immobilization of the limb may have been factors in causing the thrombosis which followed Ulceration occurred 1 month to 26 years after fracture

In 6 patients thrombosis followed operation on a leg in 15 *ulceration followed an infection of the leg* and in 12 a period of recumbency or inactivity Twelve patients gave a history of phlebitis shortly after an operation Treatment of varicose veins appeared to be the cause of ulceration in 15 patients Injection of varicose veins seemed to intensify chronic venous insufficiency if already present and to produce it if not Thrombosis from miscellaneous causes occurred in 8 patients and from no apparent cause in 19 Of 31 patients with no history of thrombosis venous stasis and ulceration might have been due to varicose veins in 29 Of the 29 24 were women of whom 17 were parous The author concludes that varicose veins may be present as a result of thrombosis but primary varicose veins rarely cause venous stasis and gravitational ulcer It is stressed that concentration on treatment of superficial varico e veins is futile

Effects of Cortisone and ACTH on Periarteritis Nodosa and Cranial Arteritis Preliminary Report Richard M Shick Archie H Baggenstoss and Howard F Polley administered cortisone to three patients with periarteritis nodosa and two with cranial arteritis and *ACTH* to two other *patients with* periarteritis nodosa Diagnoses were confirmed by biopsy

(2) P oc. Staff Meet. Mayo Cl 25 135 M 15 1950

Treatment was continuous or intermittent for 3 weeks to 4½ months Dosage schedules varied

All seven patients had prompt subjective relief Fever subsided in 24 72 hours and sedimentation rates decreased gradually to normal Partial relapses occurred in five patients after withdrawal of the hormones but improvement followed resumption of treatment Despite initial improvement two patients with periarteritis nodosa died in cardiac and renal failure Autopsy showed complete healing of all arterial lesions However in the process of healing fibrous obliteration of the lumens of the vessels had occurred resulting in widespread visceral infarction Some evidence of hypercortisonism developed in most patients during treatment

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ANTICOAGULANTS AND THROMBOEMBOLIC DISEASE

The studie of several years ago established the value of anticoagulants in preventing thromboembolic ompl cation following myocardial infarction Recent studies suggest that the routine use of dicumarol® is also indicated in patient with congestive failure Thus far there have been only a few reports dealing with the long term prophylactic administration of dicumarol® to patients in whom further thromboembolic episodes are apt to occur These preliminary reports are encouraging but the procedure should be regarded as still in the experimental stage There is evidence that certain drugs such as salicylates and sulfonam des enhance or prolong the action of dicumarol® The pract cal importance of thi in relation to long term therapy is obvious —Ed

Dicumarol® Prophylaxis of Thromboembolic Disease in Congestive Heart Failure Thromboembolic disease formerly considered largely a postoperative complication is now realized to be actually more prevalent among medical patients Patients with congestive heart failure are particularly subject to thromboembolic phenomena Difficulty in management rests not so much with therapy as with diagnosis A serious hiatus exists between clinical ability to recognize thrombosis and embolism and its actual incidence as demonstrated post mortem Since prophylactic anticoagulant therapy seems to provide the only safeguard again t this serious complication of conge tive failure W Proctor Harvey and Clement A Finch[3] (Harvard Univ) attempted to determine the safety

(3) N w E gl d J M d 4 05 11 F b 9 19)

of dicumarol® in such patients and its effectiveness in preventing thromboembolic disease

For three years patients with congestive heart failure irrespective of the heart disease were placed on dicumarol® therapy (80 patients) or in a control group (100 patients) depending on whether date of hospitalization was an even or an odd day *Age sex distribution type of heart disease* and frequency and severity of manifestations of congestive failure were similar in the two groups Attempt was made to regulate prothrombin time at approximately 30 per cent and daily prothrombin determinations were made throughout dicumarol® therapy

The impression was gained that dicumarol® can be safely administered to such patients provided the usual precautions are taken There was a total mortality rate during hospitalization of 17 per cent among controls and 9 per cent in the dicumarol® treated group Eight deaths among controls were believed on the basis of autopsy to have been due to pulmonary embolism whereas in patients given dicumarol® no deaths were believed due to embolism Deaths unrelated to thromboembolic disease were quite similar in the two groups

These data suggest that dicumarol® brought about significant reduction in thromboembolic disease and thus lowered mortality rate in patients hospitalized with congestive failure

Treatment of Repeated Embolism in Mitral Stenosis by *Long Term Administration of Dicumarol®* *Since many* patients with compensated mitral stenosis may live a long time except for the hazard of repeated embolism a means to prevent intracardiac clot formation without undue cost and risk of bleeding was welcomed in the discovery of dicumarol® as a practical anticoagulant Heparin for obvious reasons of price and inconvenience of application cannot be used for long periods but dicumarol® is inexpensive effective and its dosage can be controlled by careful prothrombin level determination in any reliable clinical laboratory As a means of preventing thromboembolic complications in mitral stenosis dicumarol® has not been used widely however

Irving Imber and Heinz Magendantz[4] (Boston) report the value of continued *dicumarol® therapy under careful super*vision in a woman aged 34 with mitral stenosis and auricular

(4) B II. New E gl J M Cent 11 151 158 August, 1949

fibrillation She had had five embolic episodes in the four months preceding dicumarol® therapy Embolic phenomena ceased after establishment and maintenance of an adequate prothrombin level

It cannot be stated certainly that dicumarol® therapy caused the sudden cessation of embolic phenomena in this patient since spontaneous remissions in such cases have been observed The sudden change from repeated serious arterial emboli during the preceding months to none after establishing the desired reduction in prothrombin level however appeared to be more than mere coincidence It is presumably necessary to continue dicumarol® therapy indefinitely in such patients

Long Term Dicumarol® Therapy is described in a case reported by Raymond L Rice Jack S Ackerman and Robert Saichek[5] (Milwaukee)

Physician 48 had an acute myocardial infarction in May 1944 A chest x ray two days later was interpreted as showing a bilateral bronchopneumonic process or changes secondary to pulmonary infarction In May 1945 he noted fever and pain in the chest which was exaggerated by deep inspiration and swallowing and persisted for two days then subsided In July 1945 he had another myocardial infarction At this time dicumarol® was given in doses adequate to keep prothrombin level between 40 and 50 per cent for the duration of his two week hospital stay Examination of lungs two days after the acute infarction revealed scattered rales over the right base posteriorly and a diagnosis of pulmonary infarction was made In August and again in September 1945 the patient experienced acute episodes of chest pain similar to the previous attacks The patient s symptoms were believed due to recurrent pulmonary emboli probably multiple in an attack and likely arising in the right ventricle It was suggested that dicumarol be continued for several months with the hope of avoiding these recurrent episodes

Dicumarol® was given from October 1945 until June 1947 when it was decided that a trial would be made without the drug In September 1947 another acute episode of chest pain occurred The patient has remained on dicumarol® therapy since that time with no recurrence of thromboembolic episodes

Biweekly prothrombin time were taken to determine adequate dosage during the first several months the drug was used Weekly dosage totaling 500 550 mg was necessary to maintain the prothrombin level within optimal limits By September 1946 a pattern of individual response to dicumarol® seemed fairly well established and weekly then biweekly and occasionally monthly estimates were made Administration of a 100 mg dose of dicumarol® followed by

(5) A I t M A 32 735 745 Ap 1 1950

two or three daily doses of 50 mg (450 500 mg /week) obtained prothrombin levels between 37 and 18 per cent from November 1947 to the time of this report Lower levels occurred only when aspirin or sulfonamides were administered At this time gingival bleeding petechiae conjunctival hemorrhages ecchymosis of the skin hematuria and bloody stools also occurred Mild gastrointestinal disturbances seemed to precede onset of hemorrhagic phenomena and consisted of distention flatulence abdominal cramps and light to clay colored stools These episodes were avoided by reducing dicumarol® dosage during salicylate or sulfonamide therapy A total of 66 300 mg dicumarol® was taken over 40 months

Treatment with Dicumarol® in Small Continuous Doses Since dicumarol® was used first in 1941 in anticoagulant therapy intermittent application has been most frequently used The characteristic features of treatment are the large maintenance doses and long intervals between doses It is common experience that this method makes it difficult to maintain prothrombin time in what is considered a therapeutically active zone Leopold Epstein and Asger Nørholm Pedersen[6] (City Hosp of Aarhus Denmark) therefore tried other forms of dosage in 37 patients in the hope of maintaining the prothrombin index within the therapeutically effective zone (between 20 and 50)

Best results were obtained with small maintenance doses of 2 cg two to four times daily depending on the individual response In 14 of 16 patients treated in this manner the prothrombin index was reduced to the desired level between 20 and 50 An advantage of this method is that fluctuations in prothrombin time are small and easily controlled by slight alteration of dose When the index approaches 20 treatment is stopped for 24-48 hours and then resumed with smaller doses Since the index varies only slightly from day to day with this type of dosage daily reading of prothrombin time is not absolutely necessary This continuous treatment is therefore more convenient for the patient simplifies hospital work and makes possible outpatient treatment with a better margin of safety

Resection of Left Auricular Appendix Prophylaxis for Recurrent Arterial Emboli is reported by John L Madden[7] (New York City)

Case 1—Woman 38 with chronic rheumatic heart disease

(6) Acta med Scand 136 313 8 1950
(7) J A M A 140 769 77 1 1 1949

with mitral stenosis auricular fibrillation and recurrent peripheral arterial emboli which had necessitated embolectomy on two occasions was chosen as the first patient for resection of the left auricular appendix During operation the heart stopped Immediate manual massage of the heart was begun together with artificial respiration The patient recovered Hemiparesis present after operation was believed secondary to a right cerebral embolus Subsequently a decided personality change was observed but examination eight months after operation disclosed personality to be normal The patient had a spastic hemiplegic gait but walked well without support Histologic examination of the specimen revealed myocardial hypertrophy fibrosis and mural thrombus of the left auricular appendix the appendix was three times normal size

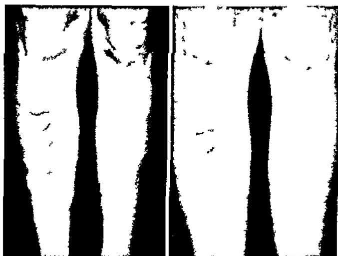
CASE 2—Man 52 was chosen for the second operation because he had had an embolic occlusion of the abdominal aorta at its bifurcation complicating chronic rheumatic heart disease with mitral stenosis auricular fibrillation and congestive heart failure Operation was uneventful Soon after operation oliguria abdominal pain and tenderness in the right upper quadrant and distention occurred but one week after operation the patient was out of bed apparently much improved However on the ninth day he complained of weakness and apprehension That afternoon he sat up to take a drink of water and suddenly died Permission for autopsy was not obtained Histologic examination of the operative specimen revealed mural thrombus of the left auricular appendix The appendix was normal in size and appearance

The commonest mode of origin of a peripheral arterial embolus is detachment of a mural thrombus located in one of the heart chambers Mural thrombi occur most frequently in cases of coronary thrombosis with myocardial infarction and in rheumatic heart disease In over 90 per cent of patients with rheumatic heart disease thrombi are located in the auricles particularly the auricular appendixes Peripheral arterial emboli occur in approximately 45 per cent of cases of rheumatic heart disease in 15 20 per cent of cases a cerebral embolus is the immediate cause of death Madden suggests resection of the left auricular appendix as a prophylaxis for recurrent arterial emboli The one indication for operation is one or more recent peripheral arterial embolic occlusions in a patient with rheumatic heart disease and mitral stenosis with or without auricular fibrillation

Early Sign of Femoral Thrombosis Gerald H Pratt[8] (St Vincent s Hosp New York City) noted three dilated sentinel veins over the tibia in over 80 per cent of patients

(8) J A M A 140 476 477 J 4 1949

with pathologic clotting (Figs 92 and 93) It has been proved that the thrombosis which causes pulmonary embolism originates in most instances in veins of the calf and progresses to the popliteal vein The first veins to dilate owing to this obstruction are the ones opening directly into the popliteal vein particularly branches of the anterior tibial vein The three small veins over the tibia empty into the saphenous and



F g 92 (l ft) —S nt n l n d l t d th t b a a [g f th mbo
F g 93 (ght) —S t l n Th p on th ght l g p l d th t on th l ft by two d
(C t y of P tt G H J A M A 140 476 477 J 4 1949)

the anterior tibial vein system are superficial and unsupported by musculature and therefore dilate very early

This sign was noted 84 times in 109 instances of thrombosis and led to an early diagnosis Other early diagnostic points are pain in the popliteal space or calf tenderness over the involved vein areas slight cyanosis of the part compared to the other parts abnormally elevated pulse rate and temperature fear of impending disaster (many patients are aware that something is wrong) very mild edema and a small nonfatal embolism (25 per cent of patients have a small embolism before a fatal one)

Fat Embolism *J E Dunphy (Boston) and Frederic W Ilfeld*[9] (Los Angeles) discuss the value of x ray in diagnosis

(9) Am J S g 77 73 743 J 1949

and of oxygen in treatment of fat embolism Three conditions are necessary for development of fat embolism (1) liquid fat free in tissues (2) torn and patent veins and (3) increased local tissue pressure above the level of venous pressure Such factors may arise after fractures blast injuries burns extensive contusion of subcutaneous tissue or surgery

When fat enters the circulation it is carried first to the lungs Some is squeezed through the pulmonary circuit and then distributed It appears to be well tolerated by most organs except the brain It is likely that small amounts of fat enter the circulation frequently though fat embolism as a principal cause of death is rare

Presence of fat embolism should be suspected when injury to bone especially simple fractures of the tibia or femur or extensive soft tissue injuries or surgical procedures in which large amounts of fat are excised or unduly traumatized is followed by an interval free of symptoms which may vary from a few hours to 9 or 10 days and then by onset of pulmonary or cerebral symptoms or both Pulmonary manifestations may vary from moderate elevation of the respiratory rate with fever to severe pulmonary edema with dyspnea cyanosis and frothy sputum Cerebral signs vary from mild psychosis or confusion to clonic convulsions generalized ragidity and coma When both pulmonary and cerebral signs appear after a free interval diagnosis is almost unmistakable The combination of petechial hemorrhages in skin and mucous membranes with cerebral or pulmonary signs is also practically diagnostic Use of x ray in diagnosis may be helpful In the case reported by the authors films taken one day after onset of embolism showed diffuse clouding throughout both lungs a picture characteristic of acute pulmonary edema and similar to that after myocardial infarction Fat in urine and sputum is confirmatory diagnostic evidence

Though treatment of fat embolism is usually regarded as useless the authors found oxygen in high concentration to be of specific value Oxygen administered by closed B L B mask brought about dramatic improvement in their patient and continued to be beneficial throughout the first two weeks of illness

Acceleration of Linear Flow in Deep Veins of Lower Extremity of Man by Local Compression was proved experimen

tally by Joseph R Stanton Edward D Freis and Robert W Wilkins[1] (Boston) in studies of 20 subjects

METHOD —With the patient supine on the x ray table the entire leg from instep to upper third of the thigh was encased in a series of loosely fitting blood pressure cuffs or in an inflatable legging A needle was inserted into a distal vein on the dorsum of the foot To the needle was attached a three way stopcock and tubing leading to an infusion of normal saline solution Test substances were injected directly into the vein through the side arm of the three way stop cock After control observations were completed the limb was pres surized by inflating the garment or blood pressure cuffs at pressures of 20 or 35 mm Hg In two patients an additional needle was placed in the femoral vein just proximal to the upper margin of the in flatable garment and blood samples collected in oxalated tubes every four seconds Test substances used in carrying out these experiments were solutions of 35 per cent diodrast® 20 per cent decholin® sodium and 0 5 per cent Evans blue dye (T 1824)

Two observers noted through a fluoroscopic screen the time required for 4 cc of diodrast® to pass from the needle to a *lead marker applied to the upper third of the calf When* control observations were completed the limb was pressurized at 20 mm Hg and the procedure repeated Control mean ap pearance time was 21 78 seconds contrasted with a mean ap pearance time of 11 38 seconds during pressurization

To confirm these results by more accurate methods lead markers were fixed at specific intervals on calf and thigh and the distance between markers carefully measured so that the linear velocity in centimeters/second could be determined Se rial roentgenograms of the calf and thigh were taken at exact intervals Technical difficulties prevented this technic from yielding results that could be accurately interpreted in every experiment However in no experiment could the results be interpreted as indicating that pressurization *had decreased the* velocity of venous flow On the contrary in practically every experiment particularly when the major portion of the dio drast® entered the deep venous system of the leg velocity of flow was unquestionably increased

Additional corroborative evidence of the acceleration of venous flow during application of pressure was obtained by foot to tongue (decholin®) circulation times in six cases Cir culation times in all instances during pressurization were de creased Limb venous circulation time was estimated in two

(1) J Cl In e t at n 8 553 558 Ma 1949

patients before and during application of pressure by measuring concentration of injected dye in consecutive four second samples from the femoral vein In both cases the appearance time of the dye was decidedly decreased during application of pressure

During this investigation collateral observations were made on size and shape of leg veins In young persons the deep veins of the calf were usually narrow and straight whereas in older persons the deep veins frequently exhibited saccular dilatations Veins well filled with diodrast® as viewed in serial roentgenograms frequently exhibited a measurable decrease in diameter during local compression Application of pressure usually did not alter distribution of diodrast® between superficial and deep veins but accelerated the flow in both Increasing pressure from 20 to 35 mm Hg did not cause a perceptible further increase in velocity of venous flow In six patients the velocity of venous flow was similarly accelerated whether the source of local compression was an inflatable legging an elastic stocking or a carefully applied elastic bandage

The authors suggest that the mechanism of the increase in linear velocity of venous flow during local compression is the concomitant decrease in total cross section area of the venous beds

CEREBRAL VASCULAR DISEASE

These articles offer further evidence of the therapeutic value of stellate ganglion block in the treatment of cerebral thrombosis In view of th s the failure of cerebral blood flow to increase following such block i of interest —Ed

Emergency Treatment of Apoplexy Despite theoretical considerations which make it seem unlikely that temporary elimination of vasomotor tonus of cerebral vessels would effectively influence deranged cerebral circulation following apoplexy Geza de Takats and G W Graupner (Univ of Illinois) believe that prompt performance of sympathetic block accelerates the phase of restitution In other words in all cerebrovascular accidents surrounding the ischemic or hemorrhagic infarct is a zone of stasis vasoparalysis and exudation of plasma

On the basis of this concept the following therapeutic

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(1) J Cl In t g t 8 5 3 8 M 194

tain cases of subarachnoid hemorrhage Anticoagulant therapy may help prevent extension of the thrombus or additional emboli and formation of thromboemboli in leg veins Oxygen therapy helps prevent or decrease cerebral anoxia and edema Vitamin K in intracranial hemorrhage decrease of intracranial pressure with hypertonic sucrose or concentrated salt free albumin and use of papaverine and/or aminophylline as vasodilators to help decrease edema surrounding the lesion may all be of aid Finally stellate ganglion block is an extremely useful therapeutic tool

Paul W Searles and William K Nowill[3] (Buffalo) compiled a series of cases of cerebral vascular accidents in which they compared a group of 55 patients on whom 127 stellate ganglion blocks were performed with a control group of 158 patients Patients were completely unselected except that after some experience it was decided not to try block in those who had grossly bloody cerebrospinal fluid since it did not appear beneficial and was thought possibly to increase bleeding

Best results with stellate ganglion blocks were obtained in cases of cerebral thrombosis of recent origin 45 per cent of 31 patients showed improvement compared with 19 per cent of the controls and mortality rate was reduced from 58 to 35 per cent Of patients with cerebral embolism 37 per cent showed improvement with stellate block Among controls no patient showed complete spontaneous remission of symptoms

The usual treatment of residual defects in the chronic stage consists of physical therapeutic measures All patients in the old or chronic group of cerebral thromboses selected for stellate ganglion block had shown no improvement of muscle function on this ordinary regime Cerebral vascular occlusion had occurred at least one month before stellate ganglion block In 43 per cent of these patients there was some improvement attributable to block therapy The authors consider this treatment of value in that it decreased disability

TECHNIC—The posterior approach appears to be the safest The patient is placed on the side with the neck acutely flexed The most prominent vertebral spinous process at the base of the neck is considered to be the seventh cervical A wheal is raised 2/ cm lateral to the interspace between the seventh cervical and first thoracic spines A needle i inserted perpendicular to the skin and advanced

(3) South M J 43 29 34 M h 1950

measures are recommended in acute cerebrovascular accidents In patients with cerebral embolism an oxygen tent medication for slowing of rapid fibrillation stellate block and anticoagulants are ordered In patients with cerebral thrombosis an oxygen tent venesection in case of hypertension stellate block and release of increased cerebrospinal fluid pressure are indicated In patients with cerebral hemorrhage an oxygen tent slow spinal drainage and neurosurgical consultation for possible evacuation of clots may be considered No sympathetic block need be done In all three types of apoplexy hypertonic sucrose or concentrated albumin with 5 7½ gr aminophylline given intravenously improves cerebral edema There is some evidence that aminophylline lowers cerebrospinal fluid pressure and its use is more rational than the extreme dehydration advocated for patients with cerebrovascular accidents

The authors performed stellate injections on 50 patients and obtained good response in 41 They recommend that injections be performed daily until no further improvement is noted

Cerebral Vascular Accidents Treatment by Stellate Ganglion Blocks Until recent years therapy for victims of the so called stroke or shock was empiric and these patients either died or survived with varying degrees of residual motor disability During the past 10 years a mode of treatment has evolved which has decreased both mortality and disability in cerebral vascular disease The disease may be divided into two stages acute and chronic The acute stage consists of the premonitory period of headache dizziness drowsiness and mental confusion followed by onset of paralysis of muscles of leg arm face and speech or coma If the patient survives this period he may have chronic paralysis or muscle weakness

Treatment of patients with cerebral vascular accidents is determined by the stage of the disease In the acute stage it consists of skilled nursing care (frequent positional changes regular changes of linen to keep the patient dry treatment of pressure points oropharyngeal suction urinary bladder care adequate fluid) cautious use of sedatives and abstinence from opiates Lumbar puncture is of value as a diagnostic procedure in all cases and as a therapeutic measure in primary subarachnoid hemorrhage Antibiotics are valuable Neurosurgery may be necessary e g in ligation of the ruptured vessel in cer

cular disease or elderly patients with cerebral thrombosis Failure of cerebral blood flow to increase in these patients indicates that increased cerebrovascular resistance is not due to increased tone mediated by the sympathetic nervous system Present observations confirm those of Penfield indicating that complete removal of all sympathetic nerve fibers which enter the cranial cavity on the carotid and vertebral arteries does not appreciably reduce the number of normal intracranial perivascular nerve fibers Both studies indicate that the sympathetics do not greatly influence cerebral vascular tone

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MISCELLANEOUS

Some of the most important reports are included in this chapter The study dealing with effects of bed rest on cardiovascular function of normal subjects raises the question as to whether the harmful effects of prolonged rest in bed may not outweigh the benefits obtained in certain patient with cardiac disease The demonstration that anxiety imposes a greater load on the heart than the usual physical exertions of ordinary living has n obvious and important therapeutic implication —Ed

Effects of Bed Rest on Cardiovascular Function and Work Performance Henry Longstreet Taylor Austin Henschel Josef Brozek and Ancel Keys[5] (Univ of Minnesota) studied six healthy young men before during and after three to four weeks bed rest Performance of the cardiovascular system (at rest in the upright posture and during work) and speed co ordination and strength were measured under rigidly controlled conditions

Bed rest produced a 17 per cent decrease in heart volume and an 8 per cent decrease in transverse diameter of the heart There was a highly significant increase in resting pulse rate which averaged roughly 0 5 beats/minute/day of bed rest Pulse rate at the end of a half hour walk at 3 5 mi /hour and 10 per cent grade increased by 40 beats/minute after bed rest Bed rest had not influenced mechanical efficiency during this walk

Oxygen intake during a 90 second run at 7 mi /hour and 15 per cent grade was reduced by 730 cc oxygen or 16 per cent after 3-4 weeks bed rest This was accompanied by increases in oxygen debt and blood lactate after the run and a

(5) J Appl d Phy 1 2 2 3 239 N mbe 1949

until bony contact is made with the transverse process of the first thoracic vertebra The needle is then partially withdrawn redirected upward and medially and advanced approximately 1 cm deeper Injection of 1 2 cc of 2 per cent procaine or a 1 5 per cent metycaine® solution is done with repeated attempts at aspiration In two to five minutes an additional 5 8 cc is given Successful stellate block produces the well known Horner s syndrome and a hot dry arm and hand

Cerebral Blood Flow in Vascular Disease of Brain Observations on Effects of Stellate Ganglion Block Peritz Scheinberg[4] (Duke Univ) used the nitrous oxide technic to measure the cerebral blood flow to and oxygen utilization of the brain in 23 patients with cerebral vascular disease—either middle aged persons with hypertension and diabetes or patients with a history of cerebral vascular accident They were divided into those with and those without changes in mental status as a result of the disease The effect of unilateral stellate ganglion block on cerebral circulation was also studied in 19 subjects

Persons with hypertension and diabetes and those with cerebrovascular accidents and normal mental status were thought to have a relatively early stage of cerebrovascular disease They showed a moderate reduction in cerebral blood flow and increased arteriovenous oxygen difference with a resulting normal cerebral oxygen utilization Persons with alterations in mental status as a result of vascular disease of the brain were assumed to have a later stage Blood flow in this group showed a considerable decrease (38 per cent) over normal whereas arteriovenous oxygen and glucose differences were only slightly increased and normal respectively This change resulted in a fall in cerebral oxygen and glucose consumption

The decrease in cerebral metabolism is related to inability of the brain cells to extract more oxygen and glucose per unit of blood rather than to the low blood flow itself Poor cellular function is thought to result in some way from the progressive vascular disease This metabolic defect is probably related to the greatly increased resistance offered to the flow of blood by diseased cerebral vessels However unilateral stellate ganglion block produced no change in cerebral metabolic functions in normal persons patients with hypertensive vas

(4) Am J Med 8 139 147 F b y 1950

death in 44 states In addition physicians friends places of previous employment insurance companies and credit bureaus were consulted home addresses and neighbors were visited police searched neighborhoods and notice was put in 20 news papers and broadcast over six New England radio stations By these measures 171 patients were located Pertinent information was obtained from 151 of the 153 patients alive when located In 115 patients this included physical electrocardiographic and fluoroscopic examinations

From data collected it was concluded that neurocirculatory asthenia is usually a chronic disorder which does not interfere significantly with a patient s work or social or family life nor does it cause death In this study 12 per cent of patients recovered 35 per cent had symptoms but no disability 38 per cent symptoms with mild disability and 15 per cent symptoms and moderate or severe disability In patients with this disorder there was not a high prevalence of the diseases recently said to be caused by anxiety hypertension heart disease peptic ulcer diabetes mellitus asthma thyrotoxicosis ulcerative colitis hysteria and schizophrenia Fewer deaths occurred in the group than were statistically expected but it is not known whether this was due to the nature of the groups used for comparison or whether it is truly a feature of the disorder

Published results of therapy in apparently similar cases managed by prolonged psychotherapy psychoanalysis and other methods such as electric convulsion procedures use of ergotamine tartrate and adrenal denervation presented no consistent or conclusive evidence that patients treated by these means get along better than patients who have had little more therapy than simple reassurance and the passage of time With reference to technic of follow up studies it is concluded that it is possible to locate and obtain co operation from most patients even 20 years after the original examination and diagnosis

Neurocirculatory Asthenia (Anxiety Neurosis Neurasthenia Effort Syndrome Cardiac Neurosis) Mandel E Cohen[7] (Harvard Univ) summarizes present knowledge of the disorder the chief symptoms of which are breathlessness palpitation nervousness irritability chest discomfort fatigability

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decrease in mechanical efficiency Maximal oxygen intake was determined in two men who had decreases of 13 and 22 per cent after bed rest

Bed rest produced striking deterioration in the cardio vascular response to posture as measured by pulse rate and blood pressure changes produced by tilting to 68 degrees on a tilt table Ataxiameter studies showed that sway was definitely increased by bed rest Co ordination as measured by pattern tracing suffered a small loss as the result of bed rest whereas speed of small hand movements of medium arm and hand movements and of gross body and arm movements did not deteriorate Grip strength was not influenced by bed rest and back strength deteriorated only slightly

After bed rest the rate of recovery of various functions was roughly proportional to the extent of deterioration in bed rest Strength co ordination and postural sway returned to normal early (four days) blood lactate after exhausting work and oxygen cost of exhausting work at an intermediate time (two weeks) pulse rate during grade walking and oxygen intake during exhausting work late (between two and five weeks) and cardiovascular response to posture very late (after seven weeks) In one man the effect on the principal com ponents of fitness of a herniorrhaphy with bed rest for three weeks was of the same order of magnitude as bed rest alone

The authors concluded that the deconditioning due to bed rest has special characteristics with major loss of perform ance ocurring in the cardiovascular system

Neurocirculatory Asthenia (Anxiety Neurosis, Effort Syn drome, Neurasthenia) 20 Year Follow up Study of 173 Patients is reported by Edwin O Wheeler Paul D White Eleanor W Reed and Mandel E Cohen[6] (Harvard Univ) For purposes of this study symptoms of neurocirculatory asthenia included breathing trouble and symptoms from two of the following three groups (1) palpitation or chest pain (2) nervousness dizziness faintness attacks or spells and (3) fatigue tiredness or limitation of activity Records of all pa tients examined by White before 1928 were reviewed Of these 173 met the diagnostic criteria Patients were located by search of telephone and street directories alumni and pro fessional lists files of licenses and records of divorce and

(6) J A M A 14 878 889 M 25 1950

serious consideration of the patient s condition adequate medical examination reassurance and elimination of relevant provoking factors frightening diagnoses unnecessary therapeutic procedures such as drugs surgery and unnecessarily prolonged psychotherapy

Genesis of Heart Sounds is reviewed by Oscar Orias[8] (Cordoba Argentina) At least four sounds may occur under normal conditions during the heart cycle Two the classic first and second sounds are heard in any living person A third heart sound may be heard during early diastole in many young persons after the second sound and the fourth sound also called auricular takes place and may often be heard immediately before the first sound during auricular systole

There is experimental and clinical evidence that the following events produce vibrations contributing to formation of the first sound muscular contraction and tension of the ventricular walls at onset of ventricular systole (muscular factor) closure of the auriculoventricular valves (valvular factor) movements and distention caused by the ejection of blood from ventricles into arteries (vascular factor) and residual vibrations due to the preceding auricular contraction (auricular factor) These factors are not listed in order of their relative importance for it varies according to conditions and with the site of auscultation However almost everyone agrees that the valvular factor is the most important

Origin of the second sound is much simpler than that of the first All anatomic clinical and experimental observations have adduced proofs in favor of the idea that closure of the semilunar valves is the essential cause of the second sound which is the acoustic expression of vibrations set up at this moment in the valves in the walls of the artery and also in the blood column itself In the ordinary conditions in which auscultation is made the sounds originating in the aorta and the pulmonary artery respectively are heard as only one sound owing to summation In cases of asynchronous closure of the semilunar valve a reduplicated or split second sound is the result

The third heart sound is produced in the final moments of rapid ventricular filling The hypothesis has been advanced that the third heart sound is caused by vibrations of the ven

(8) N w E gl d J M d 241 763 769 N 17 1949

and spells of dizziness faintness or anxiety attacks There is a chronic familial form with remissions and exacerbations and there is also an acute form The disorder is characterized by appearance of many symptoms but few signs Patients may complain of choking and smothering spells rapid heart beat pain in the chest nervousness getting tired easily irritability dizziness or heart trouble Systematic and thorough questioning reveals many symptoms in addition to the chief complaint Difficulty in doing hard work is almost universal as is difficulty in handling emotion provoking situations Review of systems reveals headaches blurred vision and giddiness Breathing difficulties are almost universal Sighing respiration is characteristic Dyspnea on exertion or even while sitting down is common as is chest discomfort The first symptoms rarely appear before age 18 and rarely after 35 Approximately twice as many women as men with this disorder are seen by physicians There is a high familial prevalence

Signs of the disorder include slight and inconstant tachycardia slight tachypnea sighing respiration flushed face and neck tremor of outstretched fingers and brisk patellar and Achilles deep tendon reflexes Results of standard clinical laboratory procedures are within normal limits Course of the illness is mild in most patients There may be remissions and exacerbations Despite symptoms of palpitation breathlessness and apprehensiveness a 20 year follow up study of 173 patients revealed that they did not show an unusual incidence of diseases such as hypertension and peptic ulcer which are supposed to develop as a result of anxiety Neurocirculatory asthenia did not predispose to any other disease or to early death

There is convincing evidence that this disorder represents a fairly common diagnostic entity in contrast to most other psychiatric illnesses which are probably rare Quantitative and objective findings bear out the patients stories Patients find hard work difficult and hard work studies (judged by treadmill and 20 in step tests) show definite abnormalities They complain of poor breathing and studies of respiration show measurable abnormalities They complain of pain and *discomfort* and quantitative studies show responses to various types of discomfort at significantly lower stimulus levels

There is no specific treatment Management

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(8) N w E gl d J M d 41 763 769 N 17 1949

tricular walls caused by sudden distention by the inrush of blood from the auricles in the final moments of rapid ventricular filling By the term ventricular walls no distinction is implied between muscular and tendinous structures or valves Furthermore although the cause given is stressed as the principal one subsidiary factors should not be excluded

During auricular activity various phenomena may produce a sound Acoustic vibrations may be produced during auricular contraction by the muscular contraction itself by tension of auricular walls passage of blood through valvular orifices distention of ventricular walls by the inrush of blood from the auricles or by friction of the auricle against neighboring structures All these factors probably combine in different proportions to produce the auricular sound

In discussion William Dock stated that in his opinion the first sound originates in the auriculoventricular and the second in the semilunar valves This opinion is based on experiments in which a piezoelectric device was inserted into dogs hearts through the carotid artery or jugular vein to record the pressure synchronously with the electrocardiogram Such records show clearly that the first sound is intense only at the auriculoventricular orifice and the second sound is intense only at the aortic orifice Likewise all the third and fourth sounds and gallops are due to tension of the auriculoventricular valves The basal first sound may contain elements or rarely a distinct split sound owing to the shock in the wall of the great arteries usually in man the pulse wave causes no sound in the aorta and in dogs in which brachial and femoral vessels have normally a pulse sound the aorta has none or a very feeble one Most split first sounds are due to ventricular asynchrony The ventricular muscle is a good sound damper as is the blood itself The great vessels transmit sound fairly well

Circulatory Dynamics before and after Exercise in Subjects with and without Structural Heart Disease during Anxiety and Relaxation Ian P Stevenson Charles H Duncan and Harold G Wolff[9] (Cornell Univ) made a study of heart rate blood pressure and cardiac output before and after a standard exercise test in persons with and without structural heart disease who had varied emotional disturbances

(9) J Cl I vestg t n 28 1534 1543 N mbe 1949

In patients who were slightly disturbed emotionally average cardiac outputs were greater before and after exercise than in those who apparently were undisturbed The difference was largely attributable to increases in stroke volume In patients with striking overt anxiety symptoms average cardiac outputs were greater before and after exercise than in those who were slightly disturbed emotionally The difference was largely attributable to greater increases in heart rate Generally there was close correlation between symptoms such as dyspnea palpitations and weakness on exertion and impaired exercise tolerance

In 10 patients with structural heart disease similarly studied the same relationship was found between emotional disturbances and signs of effort intolerance The symptoms were similar to those usually associated with cardiac failure but they often disappeared with the abolition of anxiety although structural defects in the heart were still present Changes in emotional state were accompanied by changes in exercise tolerance in seven patients alterations in exercise tolerance were observed in less than an hour

The authors concluded that impaired exercise tolerance during emotional disturbances apparently results from exaggerated cardiac mobilization in response to symbolic stimuli In the early stages of cardiac mobilization increased cardiac output is mainly achieved by increases in stroke volume in more advanced stages this increase results more from excessive increases in heart rate Ordinary physical exertions of everyday life performed during periods of relaxation and security impose little extra work on the heart compared to the cardiac mobilization associated with anxiety The increased cardiac work and excessive tachycardia at rest and in response to exercise during anxiety may be related to the increased susceptibility of patients with tachycardia to development of structural heart disease

Some Cardiologic Problems of the Tropics are the subject of statistical analysis and discussion by E Garcia Carrillo[1] (San Jose Costa Rica) Among 8 000 autopsies on patients in Costa Rica mortality of 9 6 per cent was attributable to cardiovascular disease The types of cardiovascular disease which caused death were found to be in the following proportion

(1) Am J M Sc 21 619 6 5 J 1949

coronary artery 46 1 per cent rheumatic heart including calcification of aortic valve 20 per cent syphilitic heart 19 1 per cent and cardiopulmonary heart 5 per cent Rarer causes were conditions due to malnutrition ancylostomiasis and snake venoms The rarity of myocardial infarct (0 2 per cent) is attributed to the low fat and caloric content of the diet

Despite statements to the contrary rheumatic heart disease was found to be common in these inhabitants of the tropics On the other hand subacute bacterial endocarditis was rare It is thought that the persistence of infection in persons with rheumatic heart disease made them immune to bacterial endocarditis

Myocarditis from Chagas disease or malaria was not found among these patients However, heart failure frequently resulted from anemia caused by malaria or ancylostomiasis In addition the immobility of patients with ancylostomiasis predisposed them to thrombosis and embolism Although trypanosomiasis is found in Costa Rica the author had no experience with patients suffering from this disease In trypanosomiasis myocarditis results from parasitic invasion of the myocardium Diagnosis is made by complement fixation reaction

Serial electrocardiograms were made of 11 patients who had been bitten by snakes When toxic symptoms were present ECG s showed low rounded T waves depressed S T junctions and prolonged QT intervals Because muscle treated with snake venom is known to lose potassium it is suggested that the electrocardiographic changes after poisonous snake bites are the result of hypopotassemia

Tussive Syncope Observations on Disease Formerly Called Laryngeal Epilepsy, with Report of Two Cases are presented by William S McCann Robert A Bruce Frank W Lovejoy Jr Paul N G Yu Raymond Pearson Ernest B Emerson George Engel and John J Kelly (Rochester N Y)

CASE 1 —Man 42 had repeated episodes of fainting associated with coughing for the past three years When he was recumbent blood pressure was 115/88 and on standing 122/90 Results of blood studies glucose tolerance tests lumbar puncture electroencephalography and electrocardiography were normal Massage of the carotid sinus hyperventilation and venous congestion of the head produced by a pressure cuff around the neck at 50 mm Hg did not

(2) A ch I t M d 84 845 856 De mb 1949

cause syncope Fluoroscopic chest examination showed decreased diaphragmatic excursion Total lung volume was reduced to 85 per cent of the predicted value whereas the volume of residual air was 30 per cent of the total capacity An exercise tolerance test showed considerable hyperventilation and diminished respiratory efficiency

Cardiac catheterization showed the usual decrease in net pulse pressure in the right ventricle in the Valsalva maneuver with reduction in systemic pulse pressure and also the extraordinary pressures that could develop inside the right ventricle during a paroxysm of coughing Many pressures were over 200 mm Significantly high pressures were sustained long enough to demonstrate pronounced reduction in systemic arterial pressure to 60 systolic and 50 diastolic To ascertain whether the pressure in the right ventricle during coughing was entirely due to increased intrathoracic air pressure or partly due to spasm of the pulmonary artery cardiac catheterization was repeated and a bronchoscope placed in the trachea No laryngeal or bronchial obstruction was seen In these circumstances the patient was unable to perform the Valsalva maneuver He could cough with considerable expulsive force and pressure in the right ventricle rose as high as 250 mm Endotracheal air pressure after removal of the bronchoscope was as high as 200 mm with coughing Although the patient was able to maintain the Valsalva experiment for 34 seconds he did not lose consciousness

Two months later he returned for further studies He had been coughing less and had had no further syncopal attacks At this time pressures in the right ventricle and pulmonary artery were normal Diastolic pressure in the right ventricle rose to 255 mm with coughing but there was no loss of consciousness Vasodilating effects of amyl nitrite tetraethylammonium chloride and aminophylline were investigated The first two caused the sensation of peripheral tingling but no other effects After only 0 09 Gm aminophylline U S P intravenously the patient had pain in the left side of the chest aggravated by deep breathing It promptly disappeared with oxygen therapy

CASE 2 —*Man 49 had had several syncopal attacks after severe* bouts of coughing He was short and plethoric with abdominal obesity Determination of lung volumes revealed a moderate amount of emphysema with increase of residual air to 46 per cent of total capacity Cardiac catheterization revealed pressures up to 270 mm in the right ventricle with mild coughing

In Case 1 it was fairly well established that syncope and convulsions coincident with paroxysms of coughing or the Valsalva maneuver were caused by congestion of the cerebral veins decreased cardiac output and anoxemia Studies to elucidate the mechanism of the pressures in the right ventricle with coughing were inconclusive The fact that the same high pressures which occurred in the right ventricle during cough

ing were produced with a bronchoscope in the trachea pointed to the possibility of reflex spasm of the pulmonary artery Importance of nicotine inhaled during smoking in producing these reactions is suggested Application of nicotine to the sympathetic ganglions supplying the lungs of experimental animals causes vasoconstriction Whether with excessive cigaret smoking nicotine could be absorbed in sufficient quantity to cause pulmonary vasoconstriction is questioned The authors propose the term tussive syncope for this syndrome to replace the term laryngeal epilepsy because the syncopal response is dependent on circulatory disturbances due to coughing and is not due to epilepsy

Treatment of Acute Nonspecific Pericarditis with Aureomycin This condition is usually preceded by an upper respiratory tract infection or sore throat but there are no evidences of active rheumatic infection in the joints or heart Similarly other causes for pericarditis such as tuberculosis myocardial infarction and uremia are absent Onset is generally abrupt with fever malaise and substernal or precordial pain which is worse on deep breathing movement of the trunk or swallowing *Assumption of the sitting posture or leaning forward* gives partial relief from pain A pericardial friction rub is heard early and the classic electrocardiographic patterns of acute diffuse pericarditis appear in most instances Pericardial effusion may develop Treatment has been limited to bed rest and relief of symptoms until this relatively benign disease has run its course usually in two to four weeks

The possibility that acute nonspecific pericarditis might be caused by a virus and the favorable effects obtained with aureomycin in virus diseases suggested to M Taubenhaus and William A Brams[3] (Michael Reese Hosp) that this antibiotic might prove beneficial Aureomycin was administered to two patients in whom bed rest other antibiotics and other therapeutic measures *failed to give relief and to a third patient* early in the course of pericarditis Prompt and impressive improvement with rapid recovery occurred in all Though no final conclusions can be drawn from this small group the striking results are suggestive and are reported in the hope that they will stimulate others to make further studies of this comparatively rare disease

(3) J A M A 142 973 975 Ap 1 1950

Clinical Aspects of Endocardial Myxoma Situated in Left Atrium are described by Gosta Von Reis[4] (Stockholm) Neoplastic growth within the heart is a rare phenomenon in most instances being due to metastases arising from tumors elsewhere in the body Primary cardiac tumors are rare Among the latter the pedunculated endocardial myxomas seem to be the commonest the site affected usually being the left atrium

When such myxomas reach a certain size they produce a clinical picture strongly suggesting mitral defect chiefly stenosis The picture differs somewhat from that of stenosis however for the following reasons The patient s history reveals no definite cause for the alleged organic defect such as rheumatic fever sepsis etc Initially patients are but slightly inconvenienced by symptoms but as soon as signs of cardiac incompetence appear the condition is liable to prove fatal in a short time Auscultatory findings vary considerably These are probably due to changes in the topical interrelationship between the polyp and the mitral orifice Attack of Adams Stokes type seem to be an invariable feature without demonstrable transition into complete block In all probability these attacks occur when the polyp has attained such a size that it may temporarily obstruct the orifice When the patient s position is changed the polyp may slide back from the orifice circulation being re established and cerebral anemia alleviated High sedimentation rate without positive blood cultures is a frequent observation An illustrative case follows

Woman 37 had been known to have a cardiac murmur since childhood but had no symptoms until about age 30 when sudden onset of tachycardia without preceding symptoms occurred followed by palpitation and dyspnea Valvular disease was diagnosed and digitalis prescribed but fatigue and dyspnea prevented her working after age 31 There was no history of rheumatic fever At 36 diagnosis of mitral incompetence was made At that time there was a presystolic murmur in the apical area where the first sound was doubled as well as short systolic and a suggestion of diastolic murmur near the apex The second pulmonic sound was accentuated and systolic blood pressure was 105 Sedimentation rate was 56 mm

One year later dyspnea had increased markedly and there was labial cyanosis but no edema No definite cardiac murmurs were heard at this time X ray revealed a fairly pronounced enlargement of the left atrium and right ventricle as well as evidence of pulmonary stasis An electrocardiogram showed prolonged conduction time marked right ventricular preponderance and slightly expanded

(4) A t m d S d 133 214 19 1949

ing were produced with a bronchoscope in the trachea pointed to the possibility of reflex spasm of the pulmonary artery. Importance of nicotine inhaled during smoking in producing these reactions is suggested. Application of nicotine to the sympathetic ganglions supplying the lungs of experimental animals causes vasoconstriction. Whether with excessive cigaret smoking nicotine could be absorbed in sufficient quantity to cause pulmonary vasoconstriction is questioned. The authors propose the term tussive syncope for this syndrome to replace the term laryngeal epilepsy because the syncopal response is dependent on circulatory disturbances due to coughing and is not due to epilepsy.

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(3) J. A. M. A. 142:973-975, Ap. 1, 1950.

massive myocardial metastases had flattened the T wave and left P Q R and S deflections unchanged Auricular fibrillation bundle branch block atrioventricular dissociation and nodal rhythm were encountered These phenomena are particularly helpful in diagnosing cardiac metastasis

Study of Effect of Adrenocorticotrophic Hormone (ACTH) on Experimental Cardiovascular Lesions Produced by Anaphylactic Hypersensitivity Various observations have suggested that anaphylactic hypersensitivity may be an important factor in the pathogenesis of the collagen vascular diseases Because adrenal cortex hormone has produced dramatic effects in two diseases of this group Morgan Berthrong Arnold R Rich and Paul C Griffith[6] carried out experiments to determine whether it would affect development of the lesions of periarteritis nodosa the one member of the group now definitely known to be producible by anaphylactic hypersensitivity

Procedure —Forty male albino rabbits were sensitized by a single intravenous injection of 10 cc sterile horse serum/kg body weight (This sensitizing procedure has been used in studies on the experimental production of periarteritis nodosa and rheumatic like cardiovascular lesions) On the same day intramuscular injections of ACTH were begun Since quantitative response of the rabbit to ACTH is not definitely known an initial dosage/kilogram body weight about five times that given to produce therapeutic effect in man was used. Treated animals received 5 mg ACTH every six hours during the first week Then because some animals lost considerable weight dosage for these was reduced from 20 mg /24 hours to 5 mg and for the other animal to 10 mg On the thirteenth day dosage was increased to 10 mg /24 hours for animals which had exhibited the greatest weight loss and to 20 mg for the others This dosage was maintained for 15 18 days when the animals were killed

All treated and control animals showed hypersensitivity to horse serum as revealed by positive skin tests Activity of ACTH was indicated by enlargement of the adrenal glands in the treated group Average weight of the glands in this group was 47 per cent greater than that in the controls Well marked vascular or cardiac lesions or both were found in 18 of the 20 untreated controls whereas such lesions were found in only 5 of the 20 animals treated with ACTH Though these results strongly suggest that ACTH has an inhibitory effect on development of cardiovascular lesions of hypersensitivity

(6) B H J hns Hopkins H p 86 131 140 M rch 1950

P waves Blood cultures were negative despite fever and elevated sedimentation rate. Three attacks of unconsciousness during which the patient was pulseless occurred she died during a fourth attack Autopsy revealed an endocardial myxoma of the left atrium

Heart Tumors During 1937 45 Achille Piotti[5] (Univ of Zurich) observed 30 cases of tumor metastasis to the heart—23 carcinomas and 7 sarcomas Clinical diagnosis was made in two cases of pericarditis caused respectively by carcinoma and sarcoma metastasis in all other cases the observations were made at autopsy Twelve patients showed signs of cardiac insufficiency diagnosis of myocardial degeneration and cardiac insufficiency was made eight times and of myocarditis and cardiac infarct once each There were 17 men and 13 women in the series the difference due to the higher incidence of bronchial carcinoma in men In the 23 cases of carcinoma the primary tumor was found in the bronchi (six times) lungs (twice) breast kidneys stomach pancreas colon and pleura The left side of the heart was more often involved than the right Pulmonary inflammation occurred in 11 cases of which 6 were bronchial and 2 lung carcinomas Pulmonary abscess pyelonephritis and paranephritic abscess were other associated phenomena

Tachycardia was the most frequent and persistent symptom Cyanosis was present when the pulmonary artery or mitral valve was compressed by a tumor Precordial pain occurred when the metastases penetrated into the pericardium Other symptoms included gallop rhythm presystolic sound over the apex pericardial rub facial edema and edema of the upper half of the body

Electrocardiographic changes are not always due to the metastases but are sometimes associated with an inflammation (pneumonia pulmonary abscess etc) In such cases the small tumor buds in the heart have no connection with the massive electrocardiographic changes The ECG was normal in six patients and corresponded with the anatomic findings in five because the cardiac metastases were extremely small or located at an indifferent site The ECG was of the external layer type in three cases the tumor tissue had involved the pericardium In several ECG s with flattened T wave or depressed S T segment no toxic inflammatory causes could be found

(5) Cardiologia 14 129 190 1949

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(6) B ll J h H pk H p 86 131 140 Ma h 1950

further studies are necessary before such a conclusion can be regarded as established

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KIDNEY

The importance of potassium deprivation and less frequently of potassium excess in clinical medicine has begun to be realized only during the past few years The first of the following articles should therefore be read with especial care The reader s attention is also called to the articles on peritoneal irrigation and intestinal dialysis as well as to the discussions of lower nephron nephrosis —Ed

Clinical Potassium Problems are discussed by Helen Eastman Martin Maxine Wertman Leola Westover D G Simonsen and John W Mehl (Univ of Southern California) Of 390 serum potassium determinations made during one month in a large county hospital 24 per cent were low and 26 per cent were high With one exception high serum potassium values were found in patients with uremia and were due to renal retention of potassium Low serum potassium values on the surgical service were usually due to inadequate intake of potassium postoperatively resulting from prolonged use of parenteral fluids without potassium combined with nasogastric suction and alkalosis On the medical service conditions associated with low serum potassium levels were poor intake of food due to wasting diseases prolonged use of intravenous feedings without potassium diabetic acidosis under treatment Addison s disease treated with desoxycorticosterone acetate and acute pancreatitis

In the average diet there is 1 3 Gm potassium (meat nuts vegetables fruit milk) Urinary output of potassium about equals intake if cellular levels and renal function are normal Extracellular concentration though low appears necessary for activation of acetylcholine and transmission of the electric impulse along nerves or across the myoneural junction The great bulk of body potassium is in the cells where it is the major cation Two thirds of cellular potassium is bound to protein and does not diffuse The remainder passes in and out of the cell

The three mechanisms which can cause shifts in serum potassium levels are changes in intake changes in output and

(7) Cal fornia Med. 7 133 141 March 1950

shifts between cells and serum Inadequate intake of potassium is the most frequent clinical cause of low serum and cellular potassium levels Increased excretion of potassium in urine is related to increased nitrogen excretion due to any cause (increased tissue breakdown due to infection neoplasm uncontrolled diabetes starvation and traumatic and post operative states) Though normally only a small part of potassium is excreted in stool in cases of diarrhea or fistulas sizable losses may occur Shift from serum to cells occurs during nitrogen and carbohydrate anabolism Intensive insulin therapy of diabetic acidosis causes serum potassium to fall presumably because of a movement of potassium into the cell with carbohydrate Intensive glucose treatment in the non diabetic may also cause a shift of potassium into the cell In familial periodic paralysis there occurs a spontaneous shift from serum to cells Testosterone causes a shift of potassium into cells during protein anabolism Potassium moves out of the cell in both acidosis and alkalosis

In general low serum potassium levels are associated with decreased potassium concentrations in the cell There are a few exceptions In familial periodic paralysis the muscle levels of potassium are normal with a low serum level This also occurs following use of testosterone In severe dehydration in untreated diabetic acidosis the muscle levels of potassium may be low and serum levels elevated This may also occur during intravenous therapy of low serum potassium levels due to any cause Low muscle levels of potassium are found in myotonia congenita and nutritional muscular dystrophies

Symptoms and signs of low serum potassium are muscle weakness irritability paralysis tachycardia (rarely bradycardia) dilatation of the heart with gallop rhythm and electrocardiographic changes Some patients died of paralysis of respiratory muscles Muscle paralysis related to low serum potassium level usually affects first the muscles of the trunk and extremities The authors believe that patients with serum potassium levels under 12 mg/100 cc show some degree of muscle weakness Tachycardia is prominent in most patients with serum potassium levels under 10 mg/100 cc Dilatation of the heart systolic murmurs and gallop rhythm develop in some patients These signs which usually disappear rapidly

with correction of the potassium deficit suggest at least functional myocardial impairment Low serum potassium levels are associated with delayed A V conduction prolonged QT intervals and inverted low amplitude or flat rounded T wave

Symptoms and signs of high serum potassium levels are usually masked by uremia Patients with potassium levels over 35 mg /100 cc observed by the authors have all died of cardiac standstill Between serum potassium levels of 25 and 30 mg /100 cc T waves become tall and peaked At about 35 mg /100 cc P waves disappear and QRS complex widens With potassium level between 40 and 50 mg /100 cc ventricular complexes become increasingly bizarre and ventricular fibrillation develops

The authors give potassium to all patients with serum potassium levels under 10 mg./100 cc For oral administration *enteric coated tablets of potassium chloride (0 3 Gm)* and a 1 per cent solution of potassium chloride have been used For adults 4 12 Gm KCl daily is given orally in divided doses until serum deficit is corrected Potassium chloride can also be given as a retention enema (5 10 Gm as a 1 per cent solution) Potassium for intravenous or subcutaneous administration has been given as a 0 1 per cent solution of KCl Potassium chloride is prepared in vials (1 Gm in 15 cc distilled water) and added to 1 000 cc parenteral fluid which is given slowly over two three hours Correction of potassium deficit required one to four days and 7 22 Gm KCl It is routine practice to give all patients in severe diabetic acidosis if renal function is adequate 1 Gm KCl in 1 L isotonic saline intravenously at the fourth hour of therapy and 12 Gm KCl orally in divided doses during the first 24 hours starting at the *fourth hour*

Many fatalities associated with uremia are actually due to the effect of high serum potassium If the renal lesion is potentially reversible reduction of serum potassium may be lifesaving Several methods have been advocated glucose and/or insulin to shift potassium into cells large saline infusions to wash out potassium in urine or correct extracellular sodium deficits calcium to antagonize potassium effect on the heart peritoneal lavage or artificial kidney to clear potassium from serum

Relation of Glomerular Filtration Rate and Sodium Tubular Rejection Fraction to Renal Sodium Excretion Renal regulation of sodium output is presumably mediated through the rate of sodium filtration and the fraction of filtered sodium which escapes tubular reabsorption If the fraction rejected by the tubule were constant sodium output would be fixed by filtration rate and an exact linear relation would exist between the two parameters Conversely if filtration rate were constant sodium excretion would be perfectly correlated with the fraction rejected Variability in both filtration rate and rejection fraction would provide an intermediate situation in which one or other of these functions would be the major but not sole renal agent for sodium output regulation D M Green W C Bridges A D Johnson J H Lehman F Gray and L Field[8] (Univ of Washington) attempted to determine which of these situations best accorded with observations on sodium output relations in man The question of particular interest was not why one subject excreted more sodium than another but how it was accomplished and whether or not the observed differences in output could be primarily explained by variations in filtration rate or by differences in tubular reabsorption

Sixty hospitalized patients selected to provide a representative cross section of filtration rates were studied Most had essential hypertension glomerulonephritis arteriosclerotic heart disease or toxemia of pregnancy Dietary sodium intake was sufficiently varied to insure a wide range of excretion rates

There was high correlation between rate of sodium excretion and the magnitude of the tubular rejection fraction No significant relation to filtration rate was established Variations in sodium output of 10 50 fold were observed at nearly identical rates of filtration There was no evidence that the relations had been significantly influenced by use of mannitol in clearance measurements

Renal Blood Flow and Glomerular Filtrate in Initial Stage of Acute Glomerulonephritis François Reubi[9] (Univ of Bern) used the clearance method to study four patients with acute nephritis who were sent to him as soon as diagnosis was

(8) Am J Physiol 160 306-310 February, 1950
(9) Schweiz med Wchnschr 79 896 899 Sept. 24 1949

made in one the first determination was made 48 hours after the appearance of palpebral edema He has largely followed the technic of Goldring and Chasis using para aminohippurate (PAH) to determine the effective blood flow (expressed in plasma) and sodium thiosulfate for the glomerular filtrate

METHOD —The patient fasting and recumbent is given 60 90 cc of 10 per cent sodium thiosulfate and 2 cc of 20 per cent PAH and these substances diluted with physiologic serum are administered intravenously by the drip method during the entire test to insure an approximately constant blood level The bladder is provided with an indwelling catheter and is emptied and rinsed out at the end of each period of collection The two or three periods last about 20 minutes each Toward the middle of each period blood is taken A sample of urine and one of blood taken before the test serve to determine control values Analyses for PAH are done by the method of Bratton and Marshall for the thiosulfate by that of Newman and co workers

In one patient renal extraction of the hippurate was determined by catheterization of the renal vein Blood was taken simultaneously from the sound and from a peripheral vein a few minutes after injection of 4 cc PAH Renal extraction is normally 0 94 which means that the kidney of a healthy subject extracts nearly completely the PAH it receives and that the clearance of PAH (apparent flow) equal to 94 per cent of the real plasmatic flow may be assimilated without appreciable error This ceases to be true when the extraction becomes significantly lower

Reubi found that during the first and second weeks the glomerular filtrate may reach extremely low values which gradually become normal with recovery In the only patient studied on the third day it was still subnormal and did not change until later The elevation of nonprotein nitrogen seems to be proportional to the reduction of filtrate There was no relation between the size of the filtrate and the presence of edema

During the first and second weeks the apparent renal blood flow (clearance of PAH) may be normal or lowered In one case in which it was low the extraction of PAH measured by catheterization of the renal vein was also low (0 607 instead of 0 94) this means that the real flow was much higher than the apparent flow and that it is probably normal or subnormal in all cases There is often a hyperemia from the third week on There is no correlation between the renal blood flow and the arterial tension in acute nephritis

The filtered fraction of the plasma is regularly decreased

from the sixth day on It was normal on the third day in the only case in which it was measured so early The decrease in the extraction of hippurate probably indicates a temporary tubular lesion

Clinical and Pathologic Study of Renal Disease Diseases Other than Nephritis Robert Platt and J Davson[1] (Manchester Univ) studied 188 patients with renal disease Clinicopathologic diagnoses are shown in the table

Among patients with pyelonephritis a correct clinical diagnosis was usually suggested by history of chronic or recurrent

CLINICOPATHOLOGIC DIAGNOSIS IN 188 CASES OF RENAL DISEASE

Diagnosis	Cases
Glomerulonephritis	48
Pyelonephritis	26
Malignant hypertension	24
Benign hypertension	16
Periarteritis nodosa	15
Hydronephrosis	11
Diabetic glomerulosclerosis	9
Hypoplastic kidney	)
Dehydration or anoxia	10
Pregnancy kidney	2
Amyloid disease	3
Myelomatosis	3
Disseminated lupus erythematosus	2
Pheochromocytoma	1
Renal tuberculosis	1
Scleroderma	1
Miscellaneous	7

urinary infection Because urine was frequently normal or revealed no abnormality except albumin incorrect diagnosis of malignant hypertension was often made Almost two thirds of the patients were under 40 before which malignant hypertension seldom occurs When renal failure of pyelonephritis is unaccompanied by severe hypertension chronic uremic symptoms sometimes lead to a diagnosis of anemia In younger patients changes in mineral metabolism due to prolonged renal failure may produce the syndrome of renal rickets

A contracted and granular kidney is easily recognized as the result of chronic pyelonephritis when evidence of urinary obstruction such as an impacted calculus hydronephrosis or dilated ureter is also present Variation in size between the two kidneys may be helpful in diagnosis of chronic pyelone

(1) Q J Med 19 33 55 J y 1950

phritis Weights of kidneys were recorded in 14 of 26 cases of pyelonephritis In seven one kidney weighed at least twice as much as the other Average combined weights of kidneys in the 14 cases was 110 Gm compared with 152 Gm in 8 cases of slowly progressive glomerulonephritis Hypertension was present in 14 of 25 patients with pyelonephritis Because of the essentially patchy involvement of renal parenchyma by the pyelonephritic process examination of a single block of kid ney may show only changes regarded as secondary to hyper tension whereas other areas may show changes characteristic of chronic pyelonephritis Examination of numerous blocks of tissue in contracted kidneys is essential

Principal clinical criteria by which the authors distin guished the malignant type of hypertension were papilledema high diastolic blood pressure and renal failure The diagnosis is never made without the first two the third inevitably en sues unless the patient dies prematurely of cardiac or cerebral complications Most cases of so called malignant hypertension in young persons were secondary to some pre existing renal disease Clinical diagnosis of malignant (essential) hyperten sion was suggested by absence of any history of pre existing renal disease (including urinary infection) presence of hyper tension preceding albuminuria and renal insufficiency charac teristic age incidence (35 59 in present series) and family his tory of hypertension At autopsy left ventricular hypertrophy was found in all cases weight of the heart ranging from 380 to 720 Gm Left ventricular hypertrophy associated with kidneys which are scarcely if at all contracted and which show characteristic reddish yellow cortical mottling indicates malignant hypertension A history of pyrexia leukocytosis rheumatic pains etc should suggest periarteritis nodosa Careful search should be made for vascular nodules especially on coronary and mesenteric arteries and numerous organs must be sectioned

Of 11 patients with hydronephrosis 9 had hypertension In one blood pressure was materially lowered by operation but not to normal In three patients hydronephrosis was uni-lateral the other kidney showing only the changes of malig nant nephrosclerosis In presence of uremia intravenous pyelo grams were useless as kidneys at this stage were unable to concentrate diodrast * Retrograde pyelography was unjusti

fiable because of the possibility of precipitating fatal urinary infection Correct diagnosis could sometimes be made by the history or by palpation of the kidneys

The fully developed syndrome of diabetic glomerulosclerosis with gross albuminuria general edema hypoproteinemia hypertension retinopathy and renal failure is indistinguishable clinically from severe nephritis except for presence of pre-existing diabetes and for the fundus oculi which often shows a mixture of the hypertensive and diabetic types of retinopathy Heavy albuminuria with deteriorating renal function in a patient with a long history of diabetes is sufficient to establish diagnosis and to predict the finding of typical Kimmelstiel Wilson bodies in the glomeruli Clinical diabetes was proved in eight of nine patients who showed these lesions

Of nine patients with renal hypoplasia hypoplasia was unilateral in four In three of these nephrectomy was performed because severe hypertension was found with a normally functioning kidney on one side and a nonfunctioning kidney on the other In one operation resulted in complete cure in the others it was unsuccessful in relieving hypertension In each case the kidney although small had a relatively smooth surface and did not appear to be grossly contracted Therefore diagnosis of renal hypoplasia was made despite superimposed chronic pyelonephritis

In early stages the amyloid kidney usually presented a clinical picture almost indistinguishable from that of the nephrotic stage of glomerulonephritis A palpable liver or spleen is seldom observed at onset of these symptoms and correct diagnosis is suggested only by the fact that the syndrome is superimposed on chronic sepsis or tuberculosis Early diagnosis is important since the condition may clear up if the underlying disease can be radically treated otherwise renal failure and hypertension may develop

Lower Nephron Syndrome is discussed by G E Burch and C T Pay (Tulane Univ) The general clinical pattern varies little with the responsible etiologic factors which include crushing injury wound abdominal operation burn blood transfusion reaction sulfonamide intoxication heat stroke malaria poisons hemolytic anemia uteroplacental damage eclampsia acute pancreatitis and shock from various

(2) A[illegible] J [illegible] Med 31 759 772 [illegible] 194[illegible]

causes A patient with lower nephron nephrosis resulting from a crushing injury or some other cause at first appears to be in good condition but in a few hours he quickly passes into the first phase of shock Injured areas become badly swollen and loss of fluid into tissue spaces results in hemoconcentration Skin tends to be pale cold and moist although blood pressure generally remains almost normal apparently because of compensatory vasoconstriction When this vasoconstriction is no longer maintained blood pressure falls rapidly a characteristic of the second phase of shock The mortality rate is about 90 per cent once the cardinal signs of oliguria excretion of heme pigment azotemia and hypertension develop

The first or second samples of urine tested following an injury resulting in lower nephron nephrosis contain blood albumin creatine granular casts and pigment granules Specific gravity tends to become fixed at 1 010 Urine volume remains low and may even approach anuria Urine is usually acidic It is brown because of acid hematin not because of the presence of erythrocytes The pigment usually shows a broad band in the red zone signifying a metmyoglobin compound as well as two bands in the yellow green portion closely resembling those of oxyhemoglobin Excretion of pigment begins to decrease in one or two days and casts appear in the urine in large quantities Amount of urine excreted decreases progressively

Blood studies show an accumulation of urea potassium and phosphate carbon dioxide combining power progressively falls and chloride tends to decrease probably because of inability of tubules to reabsorb it The latter part of the first week is usually the critical period If the patient recovers there is sudden diuresis followed by a urinary output which gradually rises to abnormally high levels Cardiac irregularities may occur during the critical period electrocardiographic changes resembling those in potassium poisoning may be noted Though the potassium level may be greatly increased it is not known whether levels attained are sufficient to explain the electrocardiographic manifestations

Kidneys are usually swollen and increased in weight The outer surface is pale smooth and glistening and a clear or slightly bloody fluid oozes from the cut surface Cortex bulges

and is moist pale and in sharp contrast to the cyanotic appearing medulla Degeneration and necrosis involve the lower part of the nephrons inflammatory reactions develop in interstitial spaces occasionally thrombosis of and severe damage to adjacent veins occur and heme casts are found in lower portions of the tubules There are slight or no changes in upper parts of the nephrons If the patient survives 10 days degenerated tubular epithelium will probably be completely re epithelized

Although the exact mechanism for this syndrome is unknown certain facts have been established With destruction of muscle there is release of myoglobin When pigments are liberated in large quantities and cannot be metabolized in usual fashion by the liver to be excreted in bile they are excreted by the kidneys Mechanism by which pigments reach the lumen of the tubules is not clear Heme compounds are apparently concentrated or precipitated in the lower part of the nephron It has also been proposed that disturbances in renal blood flow particularly in the presence of shock are of paramount importance in diminishing renal function and in damaging the nephron Oliguria may develop because of a disturbance in glomerular filtration resulting from impairment of renal circulation tubular obstruction which interferes with rate of urinary flow or reabsorption of glomerular filtrate by damaged lower tubular portions of the nephron

If the patient has had an injury or a reaction which is known to produce lower nephron nephrosis enough fluids should be administered to maintain diuresis A large portion of the necessary fluids and carbohydrates should be given by gastric or duodenal tube Diet consisting of 150 Gm butter and 200 Gm sugar a total of 2 000 calories contains practically no protein and little potassium and phosphorus Contrary to most opinions severe to complete restriction of protein in the diet reduces protein catabolism to such low levels that after three days the daily nitrogen excretion is less than 6 Gm Alkali such as sodium bicarbonate should be given to maintain an alkaline urine Patients should be carefully watched for oliguria to avoid overloading with fluid Morphine should be given for pain and the patient should be comfortably warm but not overheated Local surgical treatment of injured areas should be carried out The role of sympa

thetic blocking or sympathectomy is still to be evaluated

Once renal failure with oliguria and progressive uremia develops relatively little can be done except for peritoneal lavage use of an artificial kidney or dialysis It is unlikely that decapsulation is of any value Peritoneal lavage i per formed by placing a catheter in an upper lateral abdominal quadrant and another in the lower contralateral abdominal quadrant and continuously running 18 24 L modified Tyrode s solution through the peritoneal cavity every 24 or 48 hours This solution has sulfadiazine heparin and penicillin added to prevent clotting and infection To remove fluid from the body the solution is made hypertonic by increasing the amount of glucose One type of artificial kidney consists of many dichotomous branching dialyzing tubes submerged in dialyzing fluid In another a large drum on which 40-45 yd of visking cellulose are wound in spiral fashion rotates pass ing the cellulose tubing through a tray of dialyzing fluid The patient s blood enters from an artery into one end and is re turned to a vein from the other end Recently gastric lavage has been advocated A special gastric tube preferably with two lumens irrigates the stomach with about 10 L of a spe cial fluid for 24 hours Rate of irrigation is about 150 drops/ minute Intestinal irrigation with saline has been carried out with a rubber tube a small balloon in its tip passed various distances down the intestinal tract

Lower Nephron Nephrosis Report of Treatment of 44 Patients by Repeated Replacement Transfusions J Dausset[3] (Paris) removed nonprotein nitrogen from the blood of anuric patients by removing large volumes of blood and re placing it with blood of donors as is done in infants with erythroblastosis fetalis Study of decrease in blood urea nitro gen level after replacement transfusion showed that replace ment with a quantity of blood equal to the total blood volume of the patient s body permitted maintenance of urea balance and replacement by a quantity equal to two times the blood volume of the patient permitted lowering of blood urea nitro gen by 33 per cent from beginning to end of the procedure and by 25 per cent the day after the procedure

Replacement transfusion was useful whatever the origin of lower nephron nephrosis but particularly so in failures due

(3) A ch Int. Med 85 416 431 March 1950

to presence in the blood stream of nondialyzable heme pigment (as in transfusion incompatibilities massive hemolysis crush syndrome or burns) or of a poison linked with a non dialyzable protein Of Dausset s 44 patients 24 had anuria from hemolytic septicemia 3 from mercury poisoning 6 post operative anuria 3 postscarlatinal nephrosis 3 anuria from hepatonephrosis of undetermined origin and 1 each from sulfonamide nephrosis intoxication with sodium chlorate oliguria following severe burn transfusion reaction and anuria during blackwater fever

Large quantities of relatively fresh blood of a compatible type are needed for replacement transfusion but this disad vantage is lessened by use of type O blood and of Witebski substances in patients with blood of type A B or AB Trans fusion reactions were identical with those occurring after ordi nary transfusions Frequency of such reactions was multiplied by a great number of donors Possibility of transmission of the virus of homologous serum jaundice was a further danger

Of the 44 patients treated 29 recovered Failures were usu ally attributable to instituting treatment too late

TECHNIC —Study of recipient s blood should include typing in Landsteiner system and the standard Rh system and systematic test ing for irregular agglutinins complete and incomplete and cross matching Bank blood was used if it had not been stored longer than a week but fresh blood stored 24 or 48 hours was preferred A half hour before the procedure patients were given 0 01 Gm mor phine sulfate and 1 5 Gm calcium gluconate was given during the procedure to prevent tetany from sodium citrate Injection of blood was done by the usual indirect transfusion using a large needle so that blood flowed freely If the venous network was well developed exsanguination was done through a second large needle coated with silicon or paraffin and introduced with the point heading distally into the largest vein available in the extremity opposite that used for transfusion Heparin (2 mg /kg body weight) was given intravenously half at the beginning and half midway in the opera tion

When a catheter of polyvinyl was used in place of a metal needle only 1 mg heparin/kg or none was needed In using the catheter Dausset preferred to make an incision in the short saphenous vein on the femoral triangle level To supply force to insure an active outflow of blood a simple transfusion pump was useful

During the procedure intake and output of blood was exactly bal anced to avoid fluctuations exceeding 10 per cent of the patient s total blood volum Blood was exchanged at a rate of 500 cc every 5 10 minutes When exsanguination was discontinued injection of

blood equal to 10 per cent of blood volume of the body (00 cc in adults) was given in excess of the amount removed to compensate for dilution of injected blood Replacement transfusion may be done early and peritoneal dialysis then undertaken for 12 24 hours To avoid formation of adhesions in the peritoneum dialysis is then di continued If urine output is not resumed and if poor condition of the patient persists a second and sometimes a third replacement transfusion should be done

Nephrotic Syndrome Natural History of Disease Lewis A Barness Gretchen H Moll and Charles A Janeway[4] reviewed records of 208 patients with the nephrotic syndrome seen in the Children s and Infants Hospitals of Boston from 1926 to 1948 Main criteria for differentiation of lipoid nephrosis (161 patients) and the nephrotic stage of chronic glomerulonephritis (47 patients) were hypertension or azotemia for longer than one month in patients with the latter disease which occurs more frequently in children over 4 Other features of the two diseases were often indistinguishable Nonetheless it was thought desirable to differentiate between them since apparently few if any patients recover from the nephrotic syndrome if evidences of glomerulonephritis are clearcut

Lipoid nephrosis was characterized by insidious onset of edema in young children usually aged 1 4 Findings included edema hypoproteinemia hypercholesterolemia and heavy proteinuria Blood pressure was sometimes elevated for short periods but rarely over one month Microscopic hematuria did not exclude the diagnosis though macroscopic hematuria was usually evidence of glomerular involvement

Symptoms and findings in lipoid nephrosis often persisted one to three years without specific therapy Exacerbations with infection followed by remissions shortly after infection and remission soon after onset of the disease were relatively common Prognosis was not related to number or duration of exacerbations Deaths before 1942 were chiefly due to intercurrent infection After 1942 with advent of antibiotics death from infection became less common and usually occurred at home presumably because treatment was not promptly instituted Of the 161 patients with lipoid nephrosis 45 died In 23 of the 28 in whom cause of death was known death was due to infection In contrast of 19 children with

(4) P d tr 3 486 503 M h 1950

chronic glomerular nephritis in whom cause of death was known 12 died of uremia and only 5 died of infection

No form of treatment for lipoid nephrosis was wholly satisfactory Paracentesis transfusion and low salt diet were the most common supportive measures used Antibiotics were valuable during infections and apparently lowered mortality It is suggested that focal sources of infection be eliminated by operation only when surgery is definitely indicated Injections of salt poor concentrated human serum albumin and induction of measles are being evaluated as methods of inducing diuresis

There was no apparent constitutional defect in these children before onset of disease and growth and development were normal after recovery Approximately one half of the patients with clinical diagnosis of lipoid nephrosis apparently recovered completely without residual disease A small number showed persistent albuminuria or hypertension It is hoped that with closer supervision of patients and adequate chemotherapy recovery figures can be significantly increased

Chronic Nephritis and Nephrosis in Children is discussed by H H Boyle and H J Hebert on the basis of a study of all children admitted to Children s Memorial and St Luke s Hospitals Chicago with diagnosis of chronic nephritis or nephrosis between January 1946 and January 1949 a total of 59 cases Differentiation between chronic nephritis and nephrosis was always attempted and was usually possible after a few weeks observation Chief criteria for differentiation were the absence of hematuria azotemia and hypertension in nephrosis and their presence in chronic nephritis Most emphasis was placed on hematuria

Etiology of chronic nephritis and nephrosis in children is unknown Onset of both is usually insidious and acute febrile infection rarely precedes onset of edema Of the 59 patients studied only 9 had had acute infection within a month before onset of symptoms

Of the 22 deaths 5 were due to acute infection The remaining 17 apparently were due to complications arising directly from the primary kidney disease These figures are in sharp contrast to those quoted before widespread use of antibiotics when most patients died of acute infection In 10

(5) M Cl North Am 34 71 94 J y 1950

of the 13 seen at autopsy gross and microscopic changes characteristic of chronic glomerulonephritis were found in the remaining 3 anatomic findings agreed closely with Fahr's original description of 'genuine' nephrosis

Early clinical findings in chronic nephritis and nephrosis are similar Age at onset varied from 1 to 13 years but only seven children were over 6 years at onset of symptoms Edema was the one outstanding symptom and dominated all others It was generalized at first later accumulated in serous cavities particularly the peritoneal cavity, and finally tended to disappear Clinical condition differed decidedly in those with chronic nephritis and those with nephrosis in the third or drying up stage During this stage children with chronic nephritis were in increasingly poor condition with gradually diminishing kidney function Children with nephrosis gradually improved during the third stage and some eventually recovered completely

Differentiation between chronic nephritis and nephrosis was done first by laboratory findings rather than by clinical symptoms All but one patient with a diagnosis of chronic nephritis had blood in the urine None with the diagnosis of nephrosis had hematuria With nonprotein nitrogen elevation the criterion for dividing the two group results were almost but not quite the same Seven children with chronic nephritis had nonprotein nitrogen levels below 35 mg/100 cc and eight of those with nephrosis had readings higher than 35 mg/100 cc In general hypertension with progressive kidney failure developed in children with chronic nephritis whereas those with nephrosis had no hypertension Kidney function as determined by ordinary function tests was impaired in chronic nephritis and not in nephrosis The authors routinely used two tests of kidney function Neither test is accurate if there is moderate or severe edema and urinary output is low because both depend on output Phenolsulfonphthalein was injected intravenously and the amount of dye excreted in 2 hours 15 minutes measured Normal kidneys excrete 80 85 per cent of the dye With progressive kidney damage of chronic nephritis excretion gradually goes down to zero A modified Mosenthal test was used to determine concentrating ability of kidneys A test period of 24 hours beginning at 7 00 a m was used The usual diet was given with 8 oz

fluid with each meal but no fluid between meals Two hour specimens were collected durin„ the day and night urine was collected separately Normal kidneys excrete specimens with specific gravity ranging from 1 015 to 1 025 Damaged kidneys did not concentrate so highly as normal and the range was also less

General treatment consists of hygienic environment sufficient rest and adequate diet Children should be hospitalized early for diagnostic measures and regulation of diet Protracted hospitalization is not advised however A child if afebrile and able to walk around should not be kept in bed because of edema For the past 2½ years the authors have used the acid ash regimen in treating these patients The three essential features of this treatment are liberal fluid intake restriction of sodium chloride and acidification of body fluids with an acid ash diet ammonium chloride and hydrochloric acid Fluid intake of 1 500 2 000 cc is maintained Sodium chloride is restricted to 1 2 Gm daily Acid ash diet is essentially a low salt high protein diet with elimination of citrus fruit juices which are alkaline ash Ammonium chloride may be given as enteric coated tablets 5 gr three times daily at first then 10 gr three times daily Dilute hydrochloric acid 5 drops three times daily is given in water or lona lac* Edema may increase during the first 7 10 days of treatment before diuresis begins Treatment should be continued three weeks Results indicate that edema responds better to this regimen than to any other It is not a cure for nephrotic edema but patients are improved clinically Those who did not have prompt diuresis with treatment did mobilize fluid into the peritoneal cavity more rapidly than those not treated

Of the 43 children in this study with chronic nephritis 22 were alive at last observation Two had made a complete clinical recovery and 20 had evidence of active nephritis Of 16 children with nephrosis 15 were alive Three of these had completely recovered and 12 had evidence of nephrosis though 6 were free from edema and clinically well except for albuminuria The striking difference in mortality between the two groups (48 8 per cent for chronic nephritis and 6 25 per cent for nephrosis) and the corresponding difference in condition of those now alive is convincing evidence that differentiation between the conditions should be attempted

Electroencephalographic Findings in Acute Nephritis are reported by James G Hughes Fontaine S Hill and Billie Camp Davis[6] (Univ of Tennessee) In 24 children with acute nephritis 164 electroencephalograms were obtained Electro encephalographic abnormalities were noted in 22 of the 24 children

Chief changes were bursts of slow frequency waves of high microvoltage instability of EEG pattern and suppression of alpha activity with increase in fast frequencies of low am plitude Character of the EEG tended to vary from day to day and could not be correlated well with the clinical condi tion of the patient However when acute nephritis persisted there was increased likelihood of EEG abnormalities with brain potentials returning to normal as nephritis receded Whether persistent EEG abnormalities endure following acute nephritis was not determined No direct correlation between degree of hypertension and EEG abnormalities was found nor was there a clear relationship to edema anemia or azotemia

Of the 24 children with acute nephritis 22 showed abnor mal brain potentials but only 12 had symptoms referable to the nervous system These observations indicate that electro encephalography offers a sensitive approach to cortical dys function in acute nephritis

Diabetic Nephropathy Focal hyalinization in intercap illary connective tissue of the kidney in diabetes mellitus was described in 1936 by Kimmelstiel and Wilson They termed the lesion intercapillary glomerulosclerosis and related it to a clinical syndrome characterized in addition to diabetes mel litus by proteinuria widespread edema hypertension and eventual renal failure The clinical syndrome is not recognized as frequently as is the kidney lesion which suggests that the glomerular changes do not always result in nephrotic hyper tension

To clarify certain questions with regard to this disease process Eugene I Zins[7] (Metropolitan Hosp New York City) reviewed 50 consecutive autopsies of diabetic men and women Controls used in estimation of histologic lesions were 50 nondiabetics of a corresponding age group with kidney in

(6) J Pediat. 36 451 459 Ap 1 1950
(7) Am. J M S 218 408 418 Octobe 1949

volvement such as benign nephrosclerosis chronic glomerulonephritis and chronic pyelonephritis

The typical lesion of intercapillary glomerulosclerosis consists of spherical dense hyalinized material between the glomerular tufts which appear homogeneous under low power All degrees of involvement may be found in one glomerulus In sections showing the lesions many glomeruli show evidence of fibrosis a lesser involvement which may progress to the typical spherical lesion In Zins s study fibrosis of the glomerulus was classified as the minimal lesion of intercapillary glomerulosclerosis Glomeruli containing occasional spherical hyalinized lesions were listed as moderately involved The lesion was considered advanced when hyalinization existed in all glomeruli

In this series glomerular disease was discovered in 82 per cent of diabetics Previous studies have placed incidence between 20 5 and 63 5 per cent Increasing recognition of the stage of fibrosis by many investigators explains the increased incidence in recent studies The control group studied affirms previous conclusions that moderate or advanced intercapillary glomerulosclerosis is rare in the absence of diabetes Only one instance was found among the 50 controls this in a woman aged 63 who died on admission Since blood sugar and urinary sugar determinations were not made possibility of diabetes cannot be excluded This case may be similar to others reported of nondiabetics who have evidence of the hyaline change of intercapillary glomerulosclerosis The minimal lesion was indistinguishable from many lesions found in nondiabetics and therefore no accurate estimate of its specificity can be made

Comparison of incidence of intercapillary glomerulosclerosis with known duration of diabetes mellitus revealed that in the group having diabetes over 15 years all had the renal complication It was not possible to relate hypertension proteinuria the nephrotic syndrome and renal failure to the degree of involvement of the kidney except in the few in whom the lesion was far advanced In the latter instance the components were usually found to make clinical diagnosis of intercapillary glomerulosclerosis obvious Before the advanced stage is reached it is only possible to speculate on the amount of focal hyaline change that is taking place It is

reasonable to assume however that the renal lesion will progress despite therapy With increase in life expectancy for controlled diabetics more awareness of the pathogenesis and pathology of this complication is needed

Necrosis of Renal Papillae is a striking pathologic lesion found at autopsy in 25 per cent of diabetic patients with acute pyelonephritis and in 2 per cent of nondiabetics with this dis ease Acute pyelonephritis occurs in 12 20 per cent of dia betics and in 3 3 per cent of nondiabetics Most nondiabetics who have papillary necrosis without pyelonephritis have uri nary tract obstruction

Edward D Robbins (Chicago) and Alfred Angrist[8] (Long Island N Y) describe 14 cases of papillary necrosis ob served at Queens General Hospital which included 13 acute cases and 1 in which healing occurred 8 being in diabetics and 6 in nondiabetics The eight diabetic patients were younger as a group (average age 57) and had a shorter clini cal course than the nondiabetics On admission two were in coma and one was stuporous Two others had glycosuria of 3-4+ but urine contained no acetone however both were thought to be in diabetic coma Striking azotemia and mod erate anemia were present in all patients in whom determina tions of blood urea level and red cell count were made Three patients died shortly after admission and the others within two months However necrosis of renal papillae is not in variably fatal as evidenced by the healing which had occurred in one patient The six nondiabetics were all over age 73 five were men with prostatism and/or urinary tract infection The average hospital stay before death was two months

Experimentally necrosis of renal papillae has been pro duced by specific chemical poisons and by fat free diets which appear to be deficient primarily in certain long chain unsatu rated fatty acids Therefore it is possible that a parallelism may exist between disturbed fat metabolism in diabetics in nondiabetics with urinary tract obstruction and sepsis and in experimental animals with fatty acid deficiency It is also pos sible that papillary necrosis may be the homologue of cortical necrosis of the kidney on the basis of altered hemodynamics with spasm of medullary vessels rather than cortical vascu lature as the significant factor in the mechanism

(8) An Int Med. 31 773 793 N mbe 1949

Effect of Febrile Plasma Typhoid Vaccine and Nitrogen Mustard on Renal Manifestations of Human Glomerulonephritis It is generally thought that remissions in the nephrotic stage of glomerulonephritis may be caused by intercurrent infection Because the febrile phase of infection may be accompanied by profound disturbance in renal hemodynamics it seems possible that both decrease in proteinuria and diuresis may be directly attributable to alteration in renal hemodynamics It has been reported that administration of one of the nitrogen mustards (HN) prevents development of the Shwartzman phenomenon in rabbits Because diffuse glomerulonephritis may be the result of immunologic alteration in renal tissue it seems conceivable that a common factor may be operative in infection and following administration of febrile plasma typhoid vaccine or HN Hence reactive factors may be present in plasma of patients with acute infections which produce remission of the nephrotic syndrome

To test these possibilities Herbert Chasis William Goldring and David S Baldwin[9] (New York Univ) explored effects of (1) pyrogenic reaction (2) infusion of plasma from patients acutely ill with pneumococcic and hemolytic streptococcic infections and (3) nitrogen mustard on protein excretion diuresis and rate of glomerular filtration in patients with diffuse glomerulonephritis In four patients daily weight 24 hour urinary volume and urinary protein excretion rate of glomerular filtration and renal plasma flow were observed

In one patient on two occasions the pyrogenic reaction induced with typhoid vaccine resulted in a decided decrease in proteinuria accompanied by decreased filtration rate the one time it was measured No diuresis occurred It seemed that the decrease in proteinuria was related to renal hemodynamic alteration manifested in part by decrease in filtration rate Two patients given plasma showed no decrease in proteinuria or diuresis Nitrogen mustard was administered intravenously to three patients proteinuria decreased in all and diuresis occurred in one

These observations indicate that reversal of renal manifestations of glomerulonephritis in man can be induced by administration of HN_2

(9) P oc Soc E p B 1 & M d 71 565 567 A gu t 1949

Influence of Dietary Protein on Function of Diseased Kidneys was studied by Hans Olaf Bang[1] (Kommunehospitalet Copenhagen) in 11 patients with glomerulonephritis or pyelonephritis Disease was stationary in nearly all cases so that variations in clearance of urea inulin and diodrast® following changes in protein content of diet could not be attributed to improvement or exacerbation of the renal lesion In most cases clearance values were determined first after a high protein diet and next after a low protein diet At least one week elapsed between change of diet and clearance experiment

In nine patients urea clearance was lower on the low protein diet than on high protein diet (average fall, 28 7 per cent of values on a high protein diet) Also inulin clearance values generally fell almost paralleling those of urea clearance (average fall 22 7 per cent) Diodrast® clearance on the other hand was not lowered significantly The two patients with poorest renal function both responded inversely to change in protein intake In both cases urea clearance and in one also inulin clearance and diodrast® clearance were lowest on the high protein diet At the same time the patients general condition seemed better on the low protein diet than on the one rich in protein

In estimating renal function by clearance determinations in patients with renal lesions it is necessary to take into account protein content of diet when using urea clearance and inulin clearance

Carbon Tetrachloride Poisoning in Man Mechanisms of Renal Failure and Recovery Jonas H Sirota (New York City) states that carbon tetrachloride poisoning whether by inhalation or ingestion is often associated with damage to the distal kidney tubules This type of acute renal failure has therefore been included among the subclassifications of lower nephron nephrosis

By means of the Fick principle renal plasma flow was determined in four patients with acute carbon tetrachloride poisoning Renal venous blood was obtained by catheterization of the right renal vein Para aminohippurate (PAH) was used as the test substance In two patients renal plasma flow and PAH renal extraction ratio were decidedly reduced in

(1) Acta med. Sc din v (s pp 234) 136 18 21 1949
(2) J Cl n Investigat on 28 141 14 \ mbe 1949

one they were normal on the 24th day and in one who had had oliguria for 17 days renal plasma flow was 592 cc/min ute on the 37th day and PAH extraction ratio continued to be depressed

It is concluded that oliguria and anuria of carbon tetra chloride poisoning and strikingly depressed renal clearances of all substances during early diuresis are the results of de cided reduction in renal blood flow and glomerular filtration as well as abnormal tubular back diffusion of filtrate It is as sumed that back diffusion plays the most important role dur ing early oliguria as decreased renal blood flow does during late oliguria and early diuresis

Recovery of renal function after acute renal failure due to carbon tetrachloride poisoning is characterized by three clini cal phases The first phase starts with cessation of oliguria and is associated with rising plasma creatinine and urea con centrations despite adequate urine flow It lasts from one to three days The second starts with a rapid decline in plasma urea and creatinine levels The third starting about the 40th day is characterized by gradual improvement in renal blood flow and glomerular filtration so that the lower limit of nor mal is reached 100 200 days after poisoning

Renal Hematuria and Hypoprothrombinemia With ad vances in urologic knowledge diagnosis of essential hema turia is less prevalent and fewer normal kidneys are being re moved Still smaller numbers may reach the pathologist when urologists recognize that such hematuria may be due to hypo prothrombinemia C Balcom Moore[3] (Walla Walla Wash) became interested in this subject after seeing two patients with unilateral hematuria associated with low prothrombin blood levels In neither patient could any cause for hypopro thrombinemia be found nor could any definite personal or family history of bleeding be elicited However variations in liver size and tenderness in one patient and a gallstone in the other may have signified some failure in synthesis of pro thrombin due to liver disease although results were normal in the one patient given liver function tests

In recent years there have been many case reports of hematuria due to dicumarol® or heparin therapy However there are only rare reports of hematuria as the first symptom

(3) J U 1 62 76 770 No mb 1949

of hypoprothrombinemia from other causes In 7 of the 14 case reports of idiopathic hypoprothrombinemia found in the literature hematuria was stated to have been present at some time In 6 of the 14 vitamin K or blood transfusions failed to give any consistent benefit In four vitamin K produced cure Hematuria was a prominent symptom in one the presenting complaint in another and the only symptom of prothrombin deficiency as in Moore s two cases in a third In contrast the reduced prothrombin level was apparently congenital in four other cases it was improved by blood transfusions but was unaffected by vitamin K Hematuria was present in two

Moore emphasizes that any patient with obscure hematuria should have a blood study including prothrombin and clot ting times as part of the urologic investigation Blood dys crasias particularly prothrombin deficiency are probably often overlooked as a cause for unilateral renal hematuria

Clinical Study of New Sulfonamide (NU 445) in Treat ment of Urinary Tract Infections Joseph A Lazarus and Lewis H Schwarz[4] (New York City) studied the effectiveness of 3 4 dimethyl 5 sulfanilamide isoxazole (NU 445) in 25 patients with urinary tract infections caused by Aerobacter aerogenes Bacillus pyocyaneus Escherichia coli Proteus morganii Proteus vulgaris Staphylococcus aureus and Strep tococcus hemolyticus Eighteen had unmixed and 7 mixed in fections There was a total of 33 infections most of which were due to B pyocyaneus or Esch coli

NU 445 was administered orally to all patients and in addition eight were treated with bladder instillations Daily oral dose varied from 4 to 16 Gm and average duration of treatment was 25 days One patient received as much as 1 680 Gm over 140 days but average total intake was 259 Gm

Infecting organisms were eradicated in 20 instances (60 6 per cent) NU 445 was ineffective in 10 (30 3 per cent) and results in the remaining 3 were equivocal A remarkably high incidence of positive responses to treatment with NU-445 oc curred in patients with B pyocyaneus and Esch coli infec tions The drug proved effective in cases in which sulfadia zine and/or streptomycin had failed to eradicate the pathogens

Solubility of NU-445 obviated the need for concomitant

(4) J U ol 61 649 657 M ch 1949

alkali medication even when large doses were administered In none of the patients was crystalluria or hematuria observed Similarly there was no evidence of deposition of crystals in the urinary tract In general NU 445 was tolerated without serious complications however treatment was discontinued in two instances because of untoward effects Urinary excretion studies showed prompt elimination of NU 445

It is concluded that NU 445 is a valuable adjuvant in treatment of urinary tract infections caused by B pyocyaneus and Esch coli

Oral Administration of Aureomycin in Treatment of Urinary Infections is reported by Alexander M Rutenburg and Fritz B Schweinburg[5] (Boston) Aureomycin 2 Gm orally was given daily in divided doses for four to six days or longer to an unselected group of 26 patients with acute and chronic urinary infections including 5 with chronic renal insufficiency Seventeen had been treated with other antibiotics without clinical or bacteriologic improvement Twenty had one or more of the following complications hydronephrosis calculi ureteral stricture and prostatic obstruction Twenty one of the infections were due to a single organism and five to more than one Organisms involved were Escherichia coli (8 cases) Aerobacter aerogenes (12 cases) Pseudomonas aeruginosa (11 cases) Proteus vulgaris (1 case) hemolytic Staphylococcus aureus (1 case) and Streptococcus faecalis (1 case)

Sixteen patients were promptly cured by a single course of oral aureomycin Several courses were required for the three patients who had recurrent infection In these and in one patient with a vesicovaginal fistula the underlying disease had not been dealt with successfully All the patients in this series had clinical improvement even the seven in whom bacteria was not eradicated (in one Esch coli and in six Ps aeruginosa) There was exact correlation between bacterial sensitivity in vitro and immediate bacteriologic response regardless of whether the complicating disease was dealt with successfully In the latter cases recurrence or reinfections were to be expected and in fact occurred Such patients can not be permanently cured by any antibiotic In no case did bacterial resistance to the drug develop during treatment

(5) New England J Med 241 698 700 N 3 1949

Aureomycin orally was as effective as previous administration of the drug intramuscularly in another series of patients

Conservative Treatment of Anuric Uremia In a case of anuria G M Bull A M Joekes and K G Lowe[6] (London) recommend that the physician first exclude obstruction distal to the renal pelvis and factors outside the kidney such as general circulatory disturbances and alkalosis which may produce renal failure All others are treated along the lines to be indicated Unless terminal nephritis or nephrosclerosis is the cause of anuria recovery may occur Reversible causes of anuria include lower nephron nephrosis from mismatched blood transfusion crush syndrome intravascular hemolysis from various causes postabortion anuria and the lesion following protracted shock toxic nephrosis from poisoning by mercury carbon tetrachloride phenol etc and acute nephritis

TREATMENT—To prevent waterlogging which is common fluid intake is limited to the amount of water usually lost by routes other than the kidney (about 1 L) Because there is no pathway for electrolyte excretion other than the kidney diet is electrolyte free until diuresis starts While the patient is still anuric no attempt is made to correct the electrolyte disturbances since administration of potassium may cause sudden death from cardiac arrest and excess of sodium is probably harmful in other ways Because end products of protein metabolism other than urea are possibly toxic it is desirable to depress nitrogen metabolism as much as possible Since nausea is common in anuric patients they are fed through a permanently indwelling stomach tube and are given 400 Gm glucose and 100 Gm fat daily This 2 500 calorie protein free and mineral free diet can be taken with little discomfort for periods up to three weeks On admission a stomach tube is passed through the nose Through this tube a mixture of the following ingredients is permitted to drip at a steady rate 24 hours a day 400 Gm glucose 100 Gm peanut oil sufficient acacia to emulsify up to 1 L water and vitamins if desired All vomit is collected filtered through lint and returned to the stomach in the same way Drip feeding should be discontinued and superseded by a low protein diet when urine output exceeds 1 L daily Because anemia is known to lead to diminished renal function fresh packed red cells are transfused if the hemoglobin concentration is below 70 per cent

The effects of this regimen were studied on control patients with no evidence of renal disease patients with reduced renal function but without anuria and patients with anuric uremia In the five controls this regimen resulted in rapid reduction of endogenous nitrogen metabolism as indicated by a

(6) Lancet 2 9 34 Aug 6 1949

steady diminution of urea nitrogen excretion Eleven patients with extreme oliguria or anuria lasting 7 21 days were treated 4 died Of the four who died two were comatose when admitted One was admitted on the eighth day of anuria having had a laparotomy and splanchnic block the previous day On the next day pneumonia developed and the abdominal wound burst open he died of these complications The fourth patient died after diuresis began probably from a cerebral abscess In no instance did extreme oliguria or anuria last for less than 7 days and one patient did not achieve an effective urinary output for 24 days Seven patients not only survived but left the hospital free from symptoms and with adequate renal function In all there was a considerable slowing of the rate of rise of blood urea level after treatment began After the same duration of anuria or at the same level of blood urea these patients were in much better general condition than previous patients who had not been on the regimen

This regimen is recommended for patients first seen early in anuria and not already waterlogged Dialysis methods because of their dangers and difficulties should be used only for patients with gross water mineral and nitrogen imbalance

Treatment of Uremia with Intestinal Dialysis is discussed by C Brun[7] (Copenhagen) The principle of intestinal dialysis is that the lumen of portions of the intestine is irrigated with suitable solutions so that noxious retention products which cannot be excreted by the kidneys pass by diffusion into irrigation fluid and are removed with it from the organism What is accomplished is a substitute for filtration

It is not known which substances produce symptoms of uremia and therefore should be removed Electrolytic disturbances play a considerable role and urea plays little primary part in development of uremic symptoms It is supposed that retention of substances such as phenols and guanidine plays a certain part perhaps in conjunction with phosphates It is now generally assumed that uremia is an intoxication from many different substances about which relatively little is known This is of great importance when effectiveness of treatment with dialysis is evaluated because analytic methods generally used are of little value

Water equilibrium in the course of intestinal dialysis can

(7) S d J Cl & L b I t g t on t 3 8 333 1949

be controlled in such a manner that great changes can be avoided or if desired considerable edema removed By varying the content of sodium and potassium chlorine and bicarbonate in irrigation fluid and in liquids given parenterally electrolyte composition of the organism can be arbitrarily changed—the concentration of ions can be increased or decreased Urea passes readily by diffusion through intestinal mucous membrane and therefore can be removed from the organism by intestinal dialysis With the exception of urea and nonprotein nitrogen there is a rise in concentration of all other retention products that have been determined

It is difficult to assess clinical effects of dialysis Though it has seemed of value in some cases beneficial effects may have been due to simultaneous blood transfusions or corrections of electrolyte imbalances Some recently reported observations seem to show that if patients are not overloaded with water and electrolytes and at the same time the energy requirements are met by means of fat and carbohydrates it is possible in anuria to obtain just as long and even longer periods of survival than are obtained with dialysis The treatment now generally recommended for acute uremia must be the high caloric regimen poor in liquid electrolytes and nitrogen If promising results of conservative treatment hold the scope of indication for active dialysis will undoubtedly be restricted Though it cannot yet be decided whether intestinal dialysis is effective investigations should be continued

Peritoneal Irrigation in Treatment of Acute Renal Failure It was demonstrated recently that patients dying of acute renal failure due to causes such as crush syndrome abruptio placentae toxemias of pregnancy transfusion reaction burn and heat stroke all show the same kidney lesion The distal segments of kidney tubules are involved and lesions vary from focal degeneration to necrosis and disintegration of epithelium This picture has been called lower nephron nephrosis Shock appears early and is easily treated but is followed by renal insufficiency George J Strean[8] (Jewish Gen l Hosp Montreal) successfully used peritoneal irrigation in a case

Woman 25 was hospitalized with a diagnosis of thrombasthenic purpura complicating pregnancy Her blood group was A Rh negative Transfusion with 500 cc whole blood was followed

(8) Am J Obst & Gynec 59 48 489 March 1950

immediately by a severe chill and temperature rise Although the donor s blood was first reported as Rh negative rechecking showed it to be Rh positive The patient went into labor and 11 hours after admission delivered a dead 7 month fetus Catheterization at delivery yielded only 2 oz bloody urine Oliguria continued urine was bloody with many granular casts and for three days despite diaphoresis hot poultices to the loins intravenous glucose ureteral catheterization and lavage of kidney pelves oliguria became more pronounced and azotemia progressed

Peritoneal irrigation was instituted The solution was run in by gravity from large flasks through a Y tube into a drip bulb through a Berkefeld filter into a U tube over a water bath at 42 C and finally into the peritoneal cavity Sump drains were inserted into each flank the inlet tube pointing toward the mesentery the outlet tube into the pouch of Douglas The latter was connected to a large graduated jar to which a suction pump was attached Maximal blood clearance was found when the rate of flow was about 60 cc /minute Composition of the irrigating fluid was varied according to demands of the patient s electrolyte balance Other supportive therapy was also used

Urinary output increased rapidly after institution of peritoneal irrigation doubling in 24 hours Abnormal urinary findings disappeared rapidly but specific gravity remained low The tubes were removed on the eleventh day A few hours before their removal the patient had a generalized convulsion which recurred despite calcium gluconate and phenobarbital therapy Because of the possibility that seizures were caused by an electrolyte shift between extra and intracellular fluids due to loss of extracellular sodium in the irrigating fluid normal saline was given intravenously with dramatic results Later when this therapy was discontinued for 36 hours seizures recurred but were again controlled promptly with saline

The patient was discharged about a month after admission and four months later urinary findings were normal with a specific gravity of 1 033 Eighteen months later when laparotomy for a large ovarian cyst was done the peritoneal cavity was found to be free from adhesions

Peritoneal irrigation in renal failure can be successful only when pathologic changes are reversible If the renal lesion is permanent one can only prolong life for a short while but if the damage is such that sufficient functioning tissue will regenerate if given time it is possible to control azotemia temporarily so that adequate kidney function can be established

Nephrotoxic Nephritis in Rats Evidence for Glomerular Origin of Kidney Antigen David H Solomon Joseph W Gardella Herbert Fanger Frances M Dethier and Joseph W Ferrebee[9] produced nephrotoxic nephritis in rats by intra

(9) J E p M d 90 267 272 S ptembe 1949

venous injection of rabbit anti rat kidney serum Rabbits were immunized by repeated intraperitoneal injections of blood free rat kidney suspensions Pools of rabbit anti rat kidney serums were partially freed of nonantibody protein by precipitation of a gamma globulin containing fraction this fraction was redissolved in saline and used as a nephrotoxic solution in place of whole serum A method for the crude separation of kidney into glomerular and tubular portions was devised and the separate portions were tested for their ability to adsorb nephrotoxin from the gamma globulin containing fraction of nephrotoxic rabbit serum

Acute nephritis when severe was characterized by heavy proteinuria edema ascites pleural effusion diarrhea anorexia emaciation elevation of blood urea nitrogen and pallor Histologic abnormalities were noted consistently only in animals which had shown severe acute nephritis while alive In these animals thickening of the basement membrane of the glomerular capillaries was the most frequent finding The membrane appeared to be widened by a combination of edema and tissue proliferation These changes were found in 35 of 45 severely nephritic rats Less frequently glomeruli exhibited increased cellularity and mild polymorphonuclear infiltration of the tuft exudation of albuminous fluid into the capsular space or early crescentic formation Colloid droplets were occasionally seen in *the epithelium of proximal convoluted tubules Coagulated* albuminous fluid and granular debris were frequently found in the tubular lumen Arteries and interstitial tissues were invariably normal

Adsorption with glomerular tissue was consistently effective in rendering the immune serum fractions no longer nephrotoxic As a rule 0 05 cc packed finely ground glomeruli was sufficient to remove an amount of nephrotoxin equivalent to that required for production of severe nephritis in one rat It is concluded that nephrotoxic serums of this type react primarily with glomerular tissue and by inference that the antigen essential for production of these antikidney serums is of glomerular origin

Effect of Protein Deficient Diet on Rat Kidneys was studied by R Eker[1] (Norwegian Radium Hosp Oslo) Rats were given a protein free basic diet of adequate caloric content with

(1) Scand a J Cl & Lab I t g t on 6 71 19 0

supplemental milk casein in desired amounts as the source of protein The kidneys were studied histologically and renal circulation was studied by injections of India ink

Necrosis and calcification starting in the ascending loop of Henle and dilatation of the tubules were observed in rats on protein deficient diets with 140 240 and 420 mg casein/100 Gm body weight/day Circulatory disturbances in the kidneys similar to those described as characteristic of the crush syndrome were found Both morphologic and functional changes observed in these experiments were related to those described as characteristic for lower nephron nephrosis

Involvement of the lower part of the nephron is comparatively rare Apparently the pathogenesis of such involvement is widely different It is not very probable that tubular damage is due primarily to circulatory changes since involvement is limited to the distal tubules That the lesions are due to some toxic metabolite which is reabsorbed or excreted in the distal tubule seems reasonable

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The Digestive System



GEORGE B EUSTERMAN M D

PART V

THE DIGESTIVE SYSTEM

DISEASES OF THE DIGESTIVE SYSTEM 1940 50

Undoubtedly greater medical progress has been made in the past half-century than in the previous 200 years Even in the past decade its momentum has not been greatly slowed despite deterrent factors inseparable from a global war Many diagnostic technics and therapeutic procedures that had their inception in the latter years of the previous decade came to fruition in whole or large part in recent years Significant as these innovations are with respect to the digestive system they are overshadowed by one of the greatest of medical discoveries the antibiotics the outstanding achievement of the decade under consideration

The Esophagus

Diaphragmatic hernia —Partial thoracic stomach (hiatal hernia) due to herniation of the upper part of the stomach through the esophageal hiatus of the diaphragm is more common than is generally realized Such possibility should be excluded in every middle aged dyspeptic in the absence of demonstrable disease in the upper part of the digestive tract or in the biliary and pancreatic system A little more than 90 per cent of patients with hiatal hernia seen in the larger medical centers were over 40 The various types of diaphragmatic hernia acquired after birth have been classified by Harrington (1948) who pointed out that esophageal hiatal hernia represents at least 95 per cent of the cases

Symptoms arising from the hernia per se are of wide variety and degree and many authorities believe there is no characteristic syndrome However Chester Jones (1941) expressed the belief that small hiatal hernias which constitute approximately 75 per cent of all hernias have a reasonably characteristic set of symptoms which under observation can be properly diagnosed Associated disease of the gallbladder or of the stomach and duo

tient with chronic recurring otherwise unexplainable dyspepsia

Peptic ulcer—The *genesis* of ulcer is still elusive Current emphasis is on the psychosomatic factor and on corrosion from acid gastric juice The psychosomatic aspect has been so much in the foreground that many physicians and laymen have come to consider the neuropsychic factor as causative of disease particularly duodenal ulcer and chronic ulcerative colitis Those disagreeing with such a concept maintain that its proponents confuse a phase of the disease with its cause although they do not minimize the importance of treatment of this phase Proof of psychogenesis is extremely difficult However much experimental and clinical evidence points to the psychosomatic nature of cardiospasm spastic or irritable colon and obviously the persistent vomiting and malnutrition which characterize anorexia nervosa

Hay Varco Code and Wangensteen (1942) produced gastric ulcer in dogs by intramuscular injection of histamine in bees wax which prolongs maximal secretion of hydrochloric acid Thus additional testimony to the great importance of acid in the genesis of ulcer was obtained Acute and subacute gastric ulcers were initiated in cats by Ivy and Roth (1944) who used caffeine in a mixture of beeswax and mineral oil

Investigations by Levin Kirsner Palmer and Butler (1948) confirmed those of Dragstedt and earlier workers that the volume of gastric secretion at night was usually highest in patients with duodenal ulcer In patients with gastric ulcer the average nocturnal volume of gastric juice was about the same as for normal subjects but the average content of hydrochloric acid was lower

Rivers and Roodenburg (1944) have shown that *radiation of pain* characterizes many penetrating or perforating ulcers Rivers (1947) description of the syndrome of peptic ulcer perforating to the pancreas is particularly enlightening

Among recent innovations in *treatment* are antacids like aluminum hydroxide in colloidal form which are not absorbed systemically and therefore do not predispose to alkalosis protein hydrolysates ion exchange resins continuous intragastric drip the psychosomatic approach and vagotomy The neutralizing or buffering effect of the various antacids singly or in combination has been the subject of numerous investigations both in vitro and in vivo by electrometric methods Adequate sus

denum is not uncommon and may be the basis of the digestive disorder The severity of the hernial symptoms is definitely related to associated complications particularly traumatic ulcer and incarceration of the stomach The diagnosis of diaphragmatic hernia broadly speaking is essentially a roentgenologic problem Although the results of surgical repair are excellent as a rule current practice is to treat medically the uncomplicated small and medium sized hernias

Esophagitis stricture and ulcer—Esophagitis and its sequelae and esophageal ulcer like hiatal hernia with which condition these lesions are frequently associated are assuming increasing importance Wangensteen and Leven (1949) have advocated gastric resection for esophagitis or stricture or both of acid peptic origin

Esophageal varices with special reference to treatment—It has been estimated that 25 per cent of patients with hepatic cirrhosis and almost all patients with Banti s disease ultimately die of hemorrhage from esophageal varices Although splenectomy injection of sclerosing substances into the varices local application of oxidized cellulose (Oxycel) intraesophageal tamponade and thrombin therapy frequently control the bleeding the ultimate results have not been satisfactory as a rule Hence the advocacy of more direct procedures such as splenorenal or portacaval shunting operations by A O Whipple (1945) and Blakemore (1948) The most direct method of management is that of Phemister and Humphreys (1947) who carried out transthoracic esophagogastric resection after splenectomy and obliteration of the varices by injection had failed to control the tendency to hemorrhage Published reports of the end results are not too reassuring

The Stomach and Duodenum

Gastritis—There are many contradictory opinions regarding the degree to which gastritis may produce symptoms and its relation to other diseases specifically ulcer and carcinoma In our experience at the Mayo Clinic and that of many other clinicians and gastroscopists hypertrophic erosive or ulcerative gastritis is one of the most important clinical types because of its simulation of peptic ulcer and because it is a source of hemorrhage or both Whatever the conviction with respect to gastritis it is wise to carry out a gastroscopic examination in every pa

jejunal ulcer following gastroenterostomy if take down of the gastroenteric stoma and gastric resection is too hazardous and last but by no means least for gastrojejunal ulceration after adequate gastric resection

Hematemesis and melena —This dramatic frequently worri some and sometimes fatal aspect of peptic ulcer holds the sus tained interest of the profession Real progress in better under standing has been made in estimation of blood loss immediate and remote prognosis factors of risk role of diet and trans fusions and indications for surgery Details concerning these fea tures are contained in the 1948 and 1949 YEAR BOOKS OF MEDI CINE

Gastric carcinoma —Attempts at earlier detection of this dread disease one of the most pressing and difficult problems confronting the medical profession are characterized by two in novations routine roentgen examination of the stomach of ap parently normal individuals and cytologic study of the gastric secretions It is doubtful whether mass screening tests will prove practicable owing to the paucity of findings However repeated examination is indicated for patients with gastric ulcer gastric polyp and atrophy of the gastric mucosa Achlorhydric patients with gastric disturbances also deserve close surveillance A reli able biologic test for cancer promises to be the ultimate solution Papanicolaou reported his investigations on cytologic diagnosis in 1946 Subsequent observations have been made by Papanico laou and Cooper (1947) Fremont Smith Graham Ruth and Meigs (1948) Graham Ulfelder and Green (1948) Anderson McDonald and Olson (1949) and Lois Platt (1949) Despite some inherent difficulties it appears that cytologic examination may prove to be of real value in the early diagnosis of gastric carcinoma

Unfamiliar gastroduodenal lesions —Unfamiliar presumably rare lesions are usually not of great concern to the rank and file of physicians However such rarity often is more apparent than real Once physicians are aware of their existence it is surprising how frequently such lesions come to light to the credit of the physician and to the benefit of the patients Three types of dis orders that command consideration are (1) hemorrhagic gastro jejunitis following gastroenterostomy in infancy for congenital pyloric stenosis (2) nonspecific granulomatous inflammation of the stomach and duodenum and (3) prolapse of gastric mucosa

tained neutralization of the acid already secreted is not possible by routine methods Recent attempts have been made to prevent acid secretion by use of drugs with atropine like effect The most promising according to Longino Grimson, Chittum and Metcalf (1950) is banthine an orally effective parasympatholytic Cummins Grossman and Ivy (1946) studied the time of healing of 69 duodenal and gastric ulcers with craters The average for the former was 37 days with a range of 16 68 days for the latter (six cases) it was 42 days with a range of 16-68 days

The ultimate results of medical treatment have been reported both here and abroad The reports of Kraup (1946) of Copenhagen Martin and Lewis (1949) of Cambridge England Raimondi and Collen (1946) and Flood (1948) are not encouraging Martin and Lewis (1949) in a study based on 10 years observation concluded that medical treatment did not influence the natural course of the disease and urged gastrectomy for all patients with peptic ulcer of 10 or more years duration preferably before age 50

The prevention of recurrences of peptic ulcer has been greatly stressed by several American authorities Althausen (1949) for example is convinced that the problem of peptic ulcer could be greatly lessened thereby He believes the most important known causes of recurrence of ulcer are physical and mental fatigue emotional disturbances dietary indiscretions and infections

Undoubtedly the most important development during the past decade from the gastroenterologic standpoint was bilateral *vagotomy* for peptic ulcer as conceived by Dragstedt and his associates in 1944 Since he published his clinical results and his illuminating experimental and physiologic investigations many reports of others have become available Proper appraisal of vagotomy has been difficult because of the claims of enthusiastic proponents on the one hand and of outspoken opponents on the other

To the impartial observer vagotomy would seem to have its greatest usefulness in combination with gastroenterostomy for duodenal ulcer when anatomicopathologic conditions do not permit gastric resection without undue risk in combination with gastroenterostomy for duodenal ulcer in the hands of the less expert surgeon especially in the unstable patient with hypersecretion and high concentration of hydrochloric acid for gastro-

Needle biopsy of the liver —Contributions by numerous authorities at home and abroad attest the expediency and safety of needle biopsy even when the intercostal approach is used The results of needle biopsy and of studies of hepatic function by no means always parallel each other Nevertheless such combined procedure plus thorough clinical study represents distinct progress in the diagnosis and treatment of hepatobiliary disease

Treatment of hepatic amebiasis with chloroquine —N J Conan Jr (1949) reported the successful treatment of seven patients with chloroquine It undoubtedly is effective and toxicity is minimal An intestinal amebacide should be used in conjunction with it

Acute pancreatitis —It is to be remembered that much of what is regarded as new in the knowledge of disease processes is a confirmation of long established facts this applies to pancreatitis as it does to other disorders However modern diagnostic and therapeutic technics permit clearer orientation as to incidence classification biochemical changes complications and treatment Elman s classification into pancreatic edema and pancreatic necrosis of the acute form in which the former predominates justifies conservatism Determination of the levels of serum and urinary amylase especially the former while symptoms are still active is essential to diagnosis Moderate elevation of serum amylase may also occur in acute biliary disease duodenal ulcer with involvement of the sphincter of Oddi acute perforating ulcer with perforative peritonitis and pancreatic carcinoma

Because of the current world wide attitude of therapeutic conservatism many articles on treatment have appeared in the past 10 years These differ in many respects although in principle the treatment is symptomatic and supportive in the main Differentiation of the acute edematous and the necrotic form or the ability to detect the transition of the former to the latter may be difficult Elman (1949) like many other surgeons has favored surgical intervention in the latter It has been his impression that acute pancreatic necrosis can be diagnosed in nearly all cases but that it must be done purely on a bedside basis

Chronic relapsing pancreatitis —The classic report by Comfort Gambill and Baggenstoss (1946) previou ly mentioned dealing with 29 confirmed cases without associated disease of the biliary or upper part of the digestive tract created a wide

through the pyloric canal into the duodenum Five cases of the second disorder have been described by Comfort Weber Bag genstoss and Kiely (unpublished) Pathologically the lesion is identical with that of regional enteritis The stomach and duo denum may be affected when the small bowel is the major seat of involvement or they may be more conspicuously involved than the small bowel

The Liver Gallbladder and Pancreas

Unprecedented accretions to our knowledge of the diagnosis and treatment of diseases of the liver and pancreas characterize the past decade Among the impelling factors to account for this were the pandemic of acute infectious hepatitis and its con geners homologous serum and inoculation hepatitis eventually determined to be of viral origin the development refinement and broadened application of hepatic function tests aspiration biopsy of the liver and improvement of the treatment regimen for hepatic cirrhosis Moreover the exposure of countless num bers of military personnel to diseases prevalent in the tropics necessitated increasing familiarity with hepatic disorders or complications that result from amebiasis bacillary dysentery malaria schistosomiasis and leishmaniasis The nature and inci dence of cirrhotic sequelae of acute viral hepatitis have been the subject of much speculation and investigation The illuminating contributions of Elman in acute pancreatitis and of Comfort and his associates in chronic pancreatitis have made the entire pro fession more conversant with these entities which is evident from numerous recent reports dealing with acute and chronic pancreatitis and pancreatic lithiasis

Tests of hepatic function —American investigators have par ticularly distinguished themselves in this field The multiplicity of tests and the composite studies of hepatic function carried out in large institutions have made it difficult for the practitioner to appraise and select those least difficult technically In H R Butt s (1949) opinion tests which may aid in differentiating intrahepatic and obstructive jaundice are the bilirubin alkaline phosphatase urobilinogen Quick prothrombin time thymol turbidity test and duodenal drainage In the absence of jaun dice tests for retention of sulfobromophthalein (bromsulfalein) dye the cephalin-cholesterol flocculation test and the thymol turbidity test are indicated

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spread renewal of interest and many subsequent reports by others confirmed their conclusions However there remains the problem of early diagnosis and treatment especially as related to the symptoms arising from insufficiency of the external secretion and the satisfactory control of pain

Tests of pancreatic function—With the elaboration and refinement of secretin the secretagogue effect of mecholyl chloride and urecholine and the development of the Agren Lagerloff double lumen tube direct examination of the duodenal contents for volume pH values concentration and total excretion of bicarbonate and enzymes has been made possible It is unfortunate that the procedure is too involved for daily practical application Opinion too is divided as to the diagnostic value It is likely that simpler dependable tests will be evolved like that of Meuther and Knight (1949)

Cytologic diagnosis of carcinoma of extrahepatic bile ducts and pancreas—B B V Lyon as early as 1923 reported finding cancer cells in the gastric secretion but this aspect of cytologic diagnosis was not pursued McNeer and Ewing (1949) diagnosed pancreatic carcinoma in two cases from presence of exfoliated cancer cells in the duodenal secretions Several months later Lemon and Byrnes (1949) reported observations on 16 cases

INTESTINAL TRACT

Small intestine—In the past decade striking progress has been made in the knowledge of the normal and also morbid physiologic processes in the pathology diagnosis and treatment of diseases of the small intestine Lack of space does not permit detailed consideration here *Use of the Miller Abbott tube or its* modifications played a considerable role

Colon and rectum—The literature is replete with articles on chronic ulcerative colitis carcinoma diverticulitis polyps and protozoal infestation but there are no outstanding new developments Much interest has been manifested in lysozyme a mucolytic enzyme present in the stomach and intestines which some observers believe may initiate the lesions of regional enteritis and chronic ulcerative colitis The investigations of Almy Kern Jr and Tulin on normal subjects confirmed the important role that emotional stress plays in the alteration of colonic function similar in degree and kind to those alterations seen in patients with irritable colon

Notes on treatment—Reports are contradictory as to the efficacy of the sulfonamides during the acute stage of bacillary dysentery However most authorities agree that they reduce the carrier rate following the acute phase Streptomycin was found to be uniformly effective in relieving the symptoms of tuberculous enteritis H H Anderson and associates (1949) have found the theoarsenites highly effective and superior to all other arsenical amebacides They are the trivalent analogues of carbarsone U S P J D Hughes (1950) administered aureomycin to a series of patients with refractory amebiasis with encouraging results However the optimal dosage schedules have not yet been established

—GEORGE B EUSTERMAN

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to be the action of gastric acids on the sensitive esophagus treatment is directed at eliminating the factor responsible for the presence of acids Therefore in cases of short esophagus and ulcer the hiatal hernia must be repaired Nonoperative treatment in this series included dietetic management dilatation of the esophageal stricture or institution of a permanent duodenal tube Such methods resulted largely in only transitory improvement In patients with esophageal and gastric ulcer removal of the gastric lesion may have a curative effect If the esophageal ulcer is caused by a possible acid production from ectopic gastric mucosa treatment must be dietary possibly with dilatation of the constricted segment Excellent results were obtained in all patients so treated

[The fact that 11 of the 27 cases (40 per cent) were in children in the first decade of life seems unusual In a series of 270 cases of esophageal hiatal hernia of the short esophagus type reported by Olsen and Harrington (J Thoracic Surg 17 189 209 April 1948) only 5 per cent were in children under 10 The prominence of vomiting and hematemesis in children has also been reported in individual instances by American observers It is much less frequent in adults especially in the absence of stricture or marked ulceration.

Although the shortened esophagus is undoubtedly of acquired origin in most adults such shortening is probably of congenital nature in children and due to circumstances brought about by delayed embryonal descent of the stomach. Thomsen s title may be misleading since the ulceration associated with short esophagus is almost invariably of the diffuse type quite distinct anatomically and morphologically from the familiar chronic peptic ulcer of the stomach This type of ulceration can only be identified by esophagoscopic examination —Ed]

Experimental Observations on Cardiospasm in Man are reported by Stewart Wolf Thomas P Almy and Catherine R Lee[2] (Cornell Univ) Fourteen subjects who complained that swallowed food seemed to stick in the retrosternal region were studied and comparison made with 20 asymptomatic controls X rays of the patients showed obstruction to the flow of barium into the stomach

The studies indicate that the dilated elongated and obstructed esophagus of cardiospasm may be the end state of a process which in early stages is reversible and which is never entirely static The principal mechanism which participates in this process is irregular contractile activity of the lower two thirds of the esophagus which fails to propel the bolus smoothly and often leads to regurgitation A second mechanism involves localized obstruction just above the cardia

(2) G st oent l gy 13 401 4 1 Nov mbe 1949

THE ESOPHAGUS

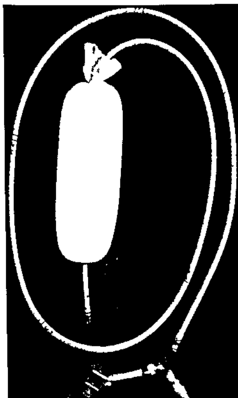
Peptic Ulcer of Esophagus can no longer be considered a rare lesion Gregers Thomsen[1] (Copenhagen) reports 27 cases seen in the University Hospital since 1936 There was no appreciable sex difference however the disease usually occurred in children under age 10 and in adults over age 30 In 18 patients the lesion coexisted with short esophagus and symptoms were vomiting hematemesis pain and difficulty in swallowing Severity of symptoms varied in children and adults In children vomiting was an outstanding complaint usually occurring immediately after or during a meal All children also had had hematemesis of varying degrees of severity It was characteristic that some children felt best when sitting because of epigastric pain or pain on swallowing when in a horizontal position In all symptoms had been present from birth or from the first months of life Adults with short esophagus and esophageal ulcer mostly complained of retrosternal pain at times radiating into the back when food passed the esophagus In addition they had difficulty in swallowing Only a few reported regurgitation and none had had hematemesis Symptoms had lasted 6 months to 10 years Nine adults with esophageal ulcer only had similar complaints In four patients the esophageal lesion coexisted with gastric or duodenal ulceration

In 21 patients characteristic ulcer craters were demonstrated on x rays In all an esophageal constriction was present around the ulcer caused in acute cases by edema and inflammatory changes and in chronic cases by fibrous changes Short esophagus with a large hiatal hernia is easily diagnosed The small hernia is more difficult to diagnose and is best looked for with the patient on his right side in the Trendelenburg position Demonstration of irregular folds of gastric mucosa above the diaphragm is decisive Esophagoscopy may confirm diagnosis although failure of the instrument to pass the constricted area is not reliable evidence for a negative diagnosis

Since the immediate cause of peptic esophagitis is thought

(1) Acta rad 1 32 193 209 1949

municates with the upper six holes of the tube and the metal tip is readjusted to communicate with the lumen containing the three lower holes By this arrangement the lumen previ ously used for suction now inflates the latex bag and the



Fg 94—P p d mod fi t f M ll Abb tt tub f ph g l tamp d d g g (C t y f B tt C B d C h S G t oe t l gy 13 144 152 A g t 1949)

three lower holes and tip are available for feeding (Fig 94)

The authors treated three patients with bleeding esophag eal varices by cardioesophageal compression A Miller Ab bott tube was passed transnasally into the stomach and dis tended with water containing 20 cc diodrast® With this pro cedure the tube is gently pulled up against the cardia until

probably due to forceful contraction of the diaphragm and reduced activity in the lower half of the esophagus Both mechanisms were observed not only in patients with cardiospasm but also in healthy persons under stress In general esophageal hypermotility and dysrhythmia were more prominent in early cases and those in which esophageal obstruction was milder and more variable In the evolution of the disorder in an individual patient one mechanism may supplant the other In only one case were x rays available from the time of onset of symptoms The series of films supports the idea that hypermotility and generalized constriction precede the stage of dilatation and atonia in the esophagus

As a group *patients with cardiospasm* are dour humorless wary suspicious noncommittal and offensive rather than aggressive in their dealings with day to day problems They are given to suppressing rather than expressing their conflicts and feelings They are circumstantial bear grudges and brood unusually over minor slights and humiliations The attitudes and behavior may be characterized as ruminative and rumination is suggested by their esophageal dysfunction In all patients in the series it was possible to correlate episodes of symptomatic exacerbation and remission with variations in life situation feeling state and attitude In the short term experimental situation variability in degree of esophageal obstruction was demonstrated in association with changes in the emotional state

[*Though definitive proof of the psychogenic origin of disease is extremely difficult* here is another good example of use of the experimental approach in an attempt to elucidate the problem Winkelstein (1944 YEAR BOOK OF GENERAL MEDICINE p 615) is convinced that in most cases cardiospasm is a psychosomatic disorder One is also reminded in this connection of those interesting and refractory cases of diffuse esophageal spasm as well as the spasms of cardia or esophagus reflexly engendered by disease of the abdominal viscera and other extraneous factors —Ed]

Management of Massive Esophageal Hemorrhage with Tamponade and Thrombin is discussed by Clair B Barnett and Sidney Cohen[3] (Wadsworth Gen l Hosp Los Angeles) Direct pressure can be exerted on the bleeding point with an inflated balloon attached to a Miller Abbott tube However the original Miller Abbott tube may be adapted so as to increase surface contact with the esophageal mucosa and to permit gavage A large latex sheath is substituted which com

(3) Gastroenterology 13 144 15 August 1949

slowly instilled through a Levin tube temporarily placed in the upper esophagus The tampon should prevent too rapid passage of thrombin past the cardia and the bleeder will be bathed in a strongly hemostatic solution During this procedure the patient should be in Fowler s position to prevent aspiration Thrombin may be used every 4-6 hours during the first 24 hours

The possibility of variceal hemorrhage is strongly suggested when other evidence of portal hypertension such as ascites splenomegaly or dilated superficial abdominal veins exist Liver failure manifested by jaundice abnormal liver function tests and hepatomegaly also supports the possibility that an upper gastrointestinal hemorrhage is secondary to ruptured varices Since cirrhotic patients may also bleed profusely it seems reasonable to discontinue tamponade if the patient continues to hemorrhage after a few hours Further tarry stools do not necessarily indicate fresh bleeding suctioned gastric contents serial blood counts and sphygmomanometer readings are better aids in deciding whether bleeding is continuing

[Any procedure wh ch gives promise of tiding over a patient in the face of such a serious emergency is very welcome It is not curative of course and presupposes ready access to the proper equipment as well as technical skill The authors properly call attention to the pioneer work of Rowntree and his a sociates (J A M A 135 630-631 Nov 8 1947) in the development of this procedure —Ed]

THE STOMACH AND DUODENUM

Phenomenon of Peptic Ulcer H Necheles[4] (Michael Reese Hosp) analyzes some established facts and most probable theories of peptic ulcer etiology The cause of ulcer is unknown The theory that hyperacidity and hypersecretion break down the resistance of gastric mucosa causing the ulcer does not adequately explain the areas of predilection in the lesser curvature and prepyloric areas of stomach and upper duodenum and the chronicity characteristic of ulcer A devitalized area must exist before digestion can occur otherwise the entire stomach and intestine would be digested

This devitalized area is most probably caused by vasocon

(4) Am. J D g t. D 16 237 242 J ly 1949

definite resistance is encountered then secured against the upper lip with adhesive tape An x ray or fluoroscopy should reveal the upper pole of the bag at the juncture of cardia and esophagus Intermittent aspiration of the gastric contents is used to detect recurrent hemorrhage Satisfactory hemostasis



Fig 95 —F lm h w g m d fi d M lle Abb tt t b tamp n g l we ph g s and b lloo g t to rd f t m ch B ll w filled w th 20 d od t a d 100 w te Dots tl ne b lloo (C t y of B r ett C B d C he S G stroe te ology 13 144 152 A g t 1949)

should be established in 24 72 hours Tamponade has been maintained for as long as 72 hours without evidence of sub sequent pressure necrosis It can be quickly re established when necessary if the balloon is deflated and the tube slipped into the antrum for a further 12 24 hours A fourth patient was treated by intraesophageal pressure using the modified tube (Fig 9_) Three patients received thrombin instillations A solution of 10 cc thrombin in water may be sipped or

denum where pH is 6 5 a level at which there is no peptic activity Acid secretion is within normal range in about half of duodenal ulcers and normal or low in most gastric ulcers Psychic disturbances may produce as well as aggravate an existing ulcer

It is suggested that gastric motility is the important factor in peptic ulcer Beneficial effects of vagotomy are due to gastric relaxation which abolishes pain and permits healing Necheles believes that vagotomy is never complete post vagotomy relapses are predicted when the stomach recovers tonus

Atropine and similar drugs have doubtful effect on the volume and acidity of secretion in the normal subject and in ulcer patients However they do lower gastric tone and motility and counteract acetylcholine vasoconstrictor acidity

[Necheles disarms criticism by stating at the outset in capital letters that the cause of ulcer is unknown And obviously he does not worship at the altar of hyperacidity But the vascular theory of ulcer genesis has increasingly fewer adherents in the light of accumulating evidence There are many straws in the wind pointing to the actual or contributing factors of the cau e or causes but at present your guess is as good as mine —Ed]

Gastric Response of Man to Acid Test Meal Following a rise of gastric acidity some process must occur to restore the acidity to resting values That duodenal regurgitation is not essential to this process has been demonstrated by aspiration of duodenal contents It has been suggested that the stomach secretes a neutral diluting fluid responsible for the reduction of acidity or that such fluid originates in the duodenum To evaluate these concepts of acid neutralization Gordon E Bermak and J Doupe[5] (Univ of Manitoba) studied the gastric secretory response to acid solution by using constant duodenal suction and phenol red to serve as an index of gastric acid dilution The results indicate that although duodenal regurgitation decreases the emptying time of the stomach it is not essential for reduction of acidity of an acid test meal It was concluded that in response to acid instillation the stomach secretes one or more substances which reduce acidity by dilution

Measurements of pH in Gastrointestinal Tract M Pantlitschko and J Schmid[6] (Univ of Vienna) determined pH in the duodenum stomach gastrectomy stump and distal loop

(5) C d J R h S t E 27 90 9 Ap 1 1949
(6) G t l g 75 138 146 1949 50

striction spasm and other vascular changes in the gastric arteries Obstruction of end arteries found in the pyloric antrum on the lesser curvature and in the duodenal bulb results in ulceration this mechanism explains the higher percentage of peptic ulcer occurring in acute or subacute form postoperatively after burns in polycythemia vera and in marantic patients

To explain the devitalized ulcerated areas in the otherwise normal person the vagus acetylcholine mechanism is offered Product of vagal effect acetylcholine increases gastric secretion and motility and causes vasoconstriction of gastric blood vessels Reduction in blood flow in the areas of predilection that are regions of end arteries may then produce hypo or anoxemia of tissue in these areas Since increased and apparently continuous vagus stimulation occurs in ulcer patients it is possible that increased or continuous vasoconstriction followed by anoxemia may be present in these areas Acute ulcer follows and under continuous vagal effect may become chronic

In favor of the acid theory of peptic ulcer are the incidence of peptic ulcer following bile or pancreatic duct ligation the Mann Williamson operation histamine in beeswax ulcer the prevention of ulcers by surgery and the effect of antacids in healing or prevention of ulcer in man and experimental animals However the experimental ulcers are acute occurring only in malnourished animals and when gastrointestinal physiology is disturbed In 10 000 dog autopsies Necheles found no instance of chronic peptic ulcer in normal animals Although antacids offer patients pain relief for several hours they neutralize gastric acidity for only short periods Alkalis affect motility more than acidity does relaxing the pylorus and duodenum and enhancing gastric emptying It is possible that chronicity hemorrhage and perforation may be related to acid pepsin concentration

Against the acid theory are the following facts Ulcers are found in the esophagus lower duodenum jejunum ileum and colon without sufficient acidity to cause digestion Duodenal ulcer occurs *in diabetes with low acidity* *Hyperchlorhydria* is often found in normal subjects and hypochlorhydria in ulcer patients Vagotomy has relieved ulcer symptoms without altering the hyperchlorhydric state Most ulcers are in the duo

in the volume of gastric juice secreted but after administration of salt solution volume and acidity increase considerably and are reduced but slightly by fasting for 24-48 hours This is in striking contrast to the great reduction in gastric secretion produced by fasting in Pavlov pouch dogs or in animals with vagally denervated total pouches Blood chemical changes reduction in gastric secretion and death seem dependent on the integrity of the vagus nerve supply to the stomach When the vagi are cut animals survive on the salt in the food and secrete small volumes of gastric juice

In most animals ulcers developed and death occurred as a result of hemorrhage or perforation In general the ulcers occurred *more rapidly in animals that secreted large volumes* of gastric juice This evidence confirms the view that pure gastric juice has the capacity to digest the wall of the stomach Preservation of vagal innervation has been essential for development of ulcers in either the whole stomach or the Pavlov pouch

Hypercalcemia without Hypercalcuria or Hypophosphatemia, Calcinosis and Renal Insufficiency Syndrome Following Prolonged Intake of Milk and Alkali. Charles H Burnett Robert R Commons Fuller Albright and John E Howard[9] studied six patients who had had prolonged and excessive intake of milk and alkali for peptic ulcer They presented hypercalcemia without hypercalcuria or hypophosphatemia normal serum alkaline phosphatase value renal insufficiency with azotemia mild alkalosis calcinosis (manifested especially by an ocular lesion resembling band keratitis) and improved on intake low in milk and alkali

Biochemical abnormalities were at first inspection those of advanced renal insufficiency but definite differences from the pattern usually seen in uremia were detected Instead of acidosis five patients had moderate alkalosis Alkalosis could not always be attributed to alkali ingestion and vomiting Serum protein levels were not as low as might have been expected and three patients had hyperproteinemia from increased serum albumin concentration

Though it was impossible to state in most instances that hyperparathyroidism did not exist many circumstances suggested that it did not These included lack of hypophospha

(9) N w E gl d J Med 240 787 794 M y 19 1949

with the aid of an antimony electrode The antimony electrode was fitted into the bulb of an Einhorn duodenal tube and from it a wool thread steeped in saturated potassium chloride solution formed an electrolyte bridge to the calomel electrode

Neutral pH values show a shift in distal direction in gastritis and gastric and duodenal ulcers Acidity in the bulb of the latter is below pH 5 Localized gastritis (antrum gastritis) shows higher acidity in the involved area of the mucous membrane than in nearby areas This causes a depression in the pH curve Food poisoning often leads to a lowering of pH a short distance beyond the papilla of Vater in addition to signs of diffuse gastritis The pH after operations on the stomach is constantly lower than normal in the distal loop This is particularly striking in cases of peptic jejunal ulcer

Secretory Studies on Isolated Stomach of dogs were carried out by Lester R Dragstedt, Edward R Woodward William B Neal Jr Paul V Harper Jr and Edward H Storer[7] (Univ of Chicago) The stomach was isolated with preservation of the blood and vagus nerve supply and quantitative collections of gastric secretion were made from *81 to 282 days* When the entire stomach was isolated and the lower end of the esophagus united to the open end of the duodenum average maximal secretion for each 24 hours was 973 cc After similar isolation with the lower end of the esophagus sutured to the side of the jejunum, average maximal secretion in each 24 hours was 906 cc When the antrum was not included with the isolated stomach but was left attached to the duodenum and sutured to the open end of the esophagus average maximal *secretion was 1 687* cc *These data support the concept* that the antrum of the stomach plays a special role in gastric secretion

Continued loss of such large amounts of gastric juice resulted in progressive hypochloremia alkalosis dehydration azotemia and death in 4 12 days when the only salt supplied was that present in the stock diet These changes can be prevented and life preserved for long periods by the intravenous injection of 1 2 L isotonic NaCl solution daily If salt replace*ment is discontinued* even after several months prompt demineralization dehydration and death follow The blood chemical changes are accompanied by a pronounced reduction

(7) Arch. S rg 60 1 20 January 1950

is overlaid with an alcoholic benzidine solution (6 Gm benzidine base in 100 cc ethyl alcohol) drop by drop to obtain a contact ring A greenish ring at the area of contact indicates a positive reaction The ring spreads into the benzidine solution immediately or in up to two minutes Intensity or gradient of color depends on the blood concentration When testing for blood in vomitus and gastric con tents water is added to either in half the volume of material used the mixture is filtered and the test carried out as before For urine when only a few red blood cells are found microscopically (4 8 red blood cells/high power field) the specimen is centrifuged the bot tom 0 1 cc containing sediment is transferred to a clean test tube 0 4 cc distilled water is added and the test is continued as before

In various ulcerative and nonulcerative gastrointestinal conditions about 32 per cent of specimens gave positive reac tions to this benzidine test 68 per cent gave positive reactions with the ordinary method Gastrointestinal carcinoma speci mens however gave 99 + per cent positive reactions with both methods The authors technic eliminates most sub stances producing false positive reactions as follows (1) fil tration of the stool suspension eliminates blood containing particles of meats (thus meat free days are unnecessary pre ceding the test) oxidase containing particles of foods par ticles of animal charcoal and insoluble metal salts (iron cop per etc) (2) the acetic acid destroys soluble oxidases Also with the contact layer or ring test soluble hemoglobin com pounds give true positive blood reactions in dilutions up to 1 100 000

[From time to time there have been modifications of the standard be zid ne and guaiac tests but reports on their clinical effectiveness in all forms of benign and malignant gastrointestinal ulcerative processes have been infrequent Such evaluation has recently been made by Hoerr Bliss and Kaufman (J A M A 141 1213 1217 Dec 24 1949) They found the benzidine and orthotoluid ne test too sensitive to be useful for rout ne testing of stools from patients who had not been prepared with a meat free d et. The guaiac test however proved sat sfactory espe c ally when performed on feces smeared directly on filter paper or on feces f om a rectal glove One d scussant of their paper favored the Alvarez and Wright modification of the Gregerson benzidine test The spectroscopic examinat on is very dependable Because we are daily be com ng more cancer consci us and because carcinoma of the gastrointes tinal tract is often accompanied by occult blood in the feces more fre quent resort to such tests should be made In fact some well known hos pitals perform them routinely when an ulcerating lesion or bleeding is under suspicion and in one inst tut on it is reputedly done on all patients with any suggest on of abdominal d sease —Ed]

Melena Study of Underlying Causes based on 293 cases of gastrointestinal bleeding in which melena was a prominent

temia accompanying the hypercalcemia lack of hypercalcuria lowering of serum calcium on low calcium intake and absence of skeletal demineralization and increased serum concentration of alkaline phosphatase Other conditions in which renal failure is often associated with hypercalcemia were excluded Such conditions are acute osteoporosis hypervitaminosis D sarcoidosis myelomatosis and generalized carcinomatosis In chronic Bright s disease with uremia acidosis with hypocalcemia and hyperphosphatemia is the usual picture

It has previously been suggested that milk and alkali adversely affect kidney function by producing alkalosis Among the authors patients no episodes of acute alkalosis with accompanying severe dehydration hypochloremia and azotemia were known to have occurred The question of whether the patients had pre existing renal disease could not be settled Prolonged hypercalcemia and renal failure such as existed in the patients studied has not previously been recorded Absence of hypercalcuria and lowering of serum calcium levels following low calcium intake suggest interference with renal secretion of calcium the mechanism of which is unknown

The pathogenesis of the condition described in the authors opinion is as follows excessive intake of milk (containing large amounts of calcium and phosphorus) and alkali kidney damage tendency to fixation in urinary calcium secretion hypercalcemia tendency to supersaturation with calcium phosphate and calcinosis

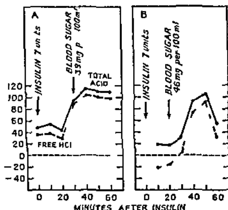
Simple Benzidine Test for Occult Blood in Feces Workers using ordinary laboratory procedures encounter many factors other than occult blood which produce positive reactions in stools of patients with suspected gastrointestinal bleeding For more accurate results M B Levin and J Y C Watt[1] (Baltimore) devised a technic which eliminates known false positive reactions

METHOD—A small portion of feces is emulsified in distilled water then passed through filter paper (Whatman no 5 or more retentive paper) into a clean test tube to obtain a clear filtrate If the filtrate is *clouded due to a breach in the paper it is refiltered* To 3 cc filtrate 8 drops of 50 per cent aqueous acetic acid or glacial acetic acid is added To the resulting mixture 8 drops of hydrogen peroxide (C P 3 per cent) is added and shaken The final mixture

(1) Rev G troe t [illegible] 16 650 651 A gu t 1949

stained with blood pigments or altered blood The occurrence of such stools usually implies that bleeding has its source in the upper digestive tract. Therefore one wonders if the term applies to bloody discharges which have their origin in lesions of the colon and rectosigmoid with rare exceptions I doubt it A slowly oozing lesion in the cecum plus lowered bowel peristalsis may give rise to melena but distal to this the stool usually is characterized as bloody or sanguinous That next to peptic ulcer bacillary dysentery was the mo t frequent cause of melena is an interesting ob ervation —Ed]

Insulin Test for Vagal Section B N Brooke[3] (Univ of Birmingham) states that when an acid secretion is obtained with an insulin test vagus nerve fibers are intact Before the



Fg 96—R p c t l 0 1 u t /kg b dy w ght *A* p pe t p *B* d fi p st p 10 d ys ft p t n V t l l p se t m ll l t f N/10 HCl N Cl q l t t 100 ml g t j (Co te y f B ook B N L c t 2 1167 1170 Dec 24 1949)

test can be regarded as satisfactory blood sugar level must be brought to 45 mg /100 ml or below

If an acid response similar to that obtained before vagal section *occurs during the early postoperative period a com* plete nerve trunk probably has been overlooked (Fig 96) There are patients however who show no response to an adequate stimulus during the first month postoperatively but secrete acid when tested six months later In this group the acid response does not show the steep rise and high final level characteristic of the preoperative pattern (Fig 97) To avoid unreliable results the tests should be done at least six months after operation After a 12 hour fast the patient is given 10

(3) Lanc t 1167 1170 D c 24 1949

clinical sign is presented by Harold Lincoln Thompson and DeVere W McGuffin" (Los Angeles) The sources of hemor rhage included all portions of the gastrointestinal tract except the anus

There were 87 cases of peptic ulcer 29 6 per cent of the entire series Hematemesis was present in 79 5 per cent Fifty five per cent of cases occurred in the fourth through the sixth decade a factor of importance when correlated with mortal ity Most patients were treated medically with a mortality of 24 9 per cent

There were 27 cases (9 per cent) in which esophageal varices were complicated by melena The highest death rate in the nonmalignant conditions—70 5 per cent—occurred in this group This fact indicates the urgent nature of gastro intestinal bleeding from this source

There were 23 cases of carcinoma of the stomach The mortality was 90 per cent in the 10 nonsurgically treated cases 33 per cent in 3 in which the lesion was resectable and 60 per cent in 10 in which it was nonresectable

Of the miscellaneous sources of hemorrhage from the stomach hiatus hernia heads the list with five cases Exclu sive of peptic ulcer there were only six cases of melena aris ing from the small intestine

Bacillary dysentery was the second most common cause of melena in this series Also of conditions localized in the large intestine it comprised the largest number 63 Signifi *cantly 73 per cent of these cases occurred within the first* decade Mortality was low

There were 18 cases of carcinoma of the rectosigmoid Mortality was 62 5 per cent in 8 cases in which surgical treat ment was employed and 90 per cent in 10 treated nonsurgi cally Other sources of bleeding from large intestine included idiopathic ulcerative colitis (16 cases) Medical treatment was given in 14 with a mortality of 35 6 per cent Surgical treat ment in two cases was successful There were 11 cases of di verticulitis of the colon of which 63 6 per cent occurred in the descending colon and sigmoid Most of the patients with di verticulitis were females Nonsurgical treatment was carried out in all without mortality

[By melena is meant the passage of dark pitchy and grumous stools

( ) *J A M A 141 1208 1213 Dec 24 1949*

Mechanism of Postgastrectomy Dumping Syndrome The stomach functioning as a reservoir normally evacuates a mixed meal in three or four hours at a rate of 10 15 cc/minute In patients deprived of a normal gastric reservoir by gastroenterostomy or subtotal gastric resection ingested food may enter the jejunum almost immediately and give rise to symptoms such as sweating tightness or pain in the epigastrium nausea weakness palpitation feeling of warmth vertigo and even collapse These symptoms the dumping syndrome may occur after all meals or only after certain meals and vary in severity Some patients find that avoidance of certain foods or of liquid may prevent symptoms

Production of symptoms has been ascribed to (1) hypoglycemia secondary to the hyperglycemia resulting from rapid absorption of carbohydrate from the jejunum (2) the hyperglycemia of the postprandial hyperglycemic phase of absorption and (3) mechanical distention of the jejunum Both early postprandial symptoms due to mechanical distention of the jejunum and late postprandial symptoms due to hypoglycemia are said to occur

To determine the mechanism of production of symptoms Thomas E Machella[5] (Univ of Pennsylvania) performed experiments on 16 patients manifesting the dumping syndrome and on control subjects with intact stomachs Diet included normal mixed meals and test meals of cooked cereal cream milk sugar toast butter and egg calculated to contain 75 Gm carbohydrate 25 Gm protein and 38 Gm fat Tests were made with hypertonic solutions of protein hydrolysate and dextri maltose[®] with glucose or sucrose given orally and intravenously and with sodium sulfate instilled in the jejunum An air inflated balloon was used to distend the intestine in some experiments Effectiveness of atropine and of fluid and sugar free meals in preventing symptoms was also studied

Symptoms occurred toward the end of or shortly after a mixed meal when hypertonic food passed into the jejunum Although hyperglycemia was associated with blood pressure rise and increased pulse rate during this period hyperglycemia did not cause the symptoms Hypoglycemia was not found in any patient during symptoms Dumping occurred after intrajejunal instillation of glucose before hyperglycemia de

(5) A S g 130 145 159 A g 194

units of insulin intravenously With this dosage the blood sugar will be depressed adequately in 82 per cent of cases Blood sugar levels are measured 30 and 40 minutes after insulin injection

For routine purposes only a postoperative test is necessary When the vagi are intact the quality and quantity of

Fig 97—Re lts f i l n t t n tw cas s m th aft g l s t w th t g st oe t tomy h w ng c d sec t o d r g n ght b fo test Immed ate p t p at t ts w eg t Te ts at m nth how d ly l ght acid I n e Ve t l al r p es ts m ll l t rs of N/10 HCl o NaCl q l nt t 10) ml gastric j (Cou te y of Brook B N La t 2 1167 1170 D 24 1949)

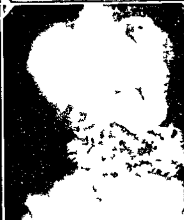
acid response to hypoglycemia bear no more relation to the ordinary acid level in the stomach than does the response to histamine Lack of acid secretion after vagotomy when the blood sugar is reduced to 45 mg or less does not make it certain that all nerve fibers have been cut

[It is to be hoped that the modification of the test and the other recommendations proposed by the author will eliminate in whole or large part the discrepancies frequently now encountered —Ed]









Fg 98 (t p l ft)—P p t e t m b b w g f ly g d t l p t l

Fg 99 (top ght)—S m p t t k ft g t my N t mpl t y th t m d l t t N p t lt w

Fg 100 (bottom l ft)—S m p t t m d y F fty p t bou t

Fg 101 (b ttom ght)—S p t t m h ft g my Good y f ton d f p t l

(C t y f I F t l Am J R tg 1 63 66 5 J y 1950)

veloped and during oral ingestion of glucose or sucrose but did not occur when glucose was injected intravenously

The dumping syndrome was also reproduced in control subjects by intrajejunal instillation of hypertonic solutions of glucose protein hydrolysate and sodium sulfate and by distention of the jejunum with an air inflated balloon To produce symptoms meals must possess ingredients of high osmotic pressure usually sugars and sufficient fluid to dissolve them and still yield a hypertonic solution Vomiting offered complete relief from symptoms by removing the cause of distention When hyperperistalsis resulted in rapid stool evacuation symptoms did not occur Omission of fluids from meals and administration of atropine in physiologic doses before meals prevented symptoms though the exact mechanism of preventive action of atropine is not clear Vagotomy does not prevent symptoms

It is suggested that the early postprandial dumping syndrome is due to distention of the jejunum by outpouring of fluid by the jejunal wall in an attempt to dilute the hypertonic food solution passed along by the nonretentive stomach rather than to mechanical distention by ingested food bulk

[The gist of this investigation was recorded in discussion of an article by Schechter and Necheles on the subject (1949 YEAR BOOK OF MEDICINE, p 706) —Ed]

Roentgen Studies of Upper Gastrointestinal Tract in Vagotomy were made in 80 male and 3 female patients aged *20 72* by Frank Isaac Richard E Ottoman and Joseph A Weinberg[4] (Birmingham Veterans Admin Hosp Van Nuys Calif) Postvagotomy check ups were possible in *75* at one week *72* at one month and *50* at six months

The most striking but the least constant change was loss of gastric tone with dilatation (Figs 98-101) Initially in the postvagotomy period *57 4* per cent showed this change after six months it was present in *33 4* per cent Delayed motility was present in 80 per cent in the early postoperative period six months later 41 per cent still had six hour retention The most constant postvagotomy change was decreased peristaltic action which was found in *87* per cent in the early postoperative period and in 48 per cent at six months After six months more patients showed complete return to normal following

(4) Am J Roentgenol 63 66 75 J u ry 19 0

simple vagotomy combined with gastroenterotomy than following simple vagotomy alone Whether the operation was performed by the thoracic or abdominal route seemed of little importance Most patients with a demonstrable ulcer crater in the duodenal bulb preoperatively showed disappearance of the niche after vagotomy

Definite alterations were noted in the pattern and motility of the small intestine as a result of vagus section (Figs 102 105) The most significant pattern changes consisted of moderate dilatation of the second and sometimes the third portion of the duodenum These changes tended to disappear after six months Delayed motility in passage of barium meal was noted consistently and showed little tendency toward improvement over six months Less constant small intestine alterations included pooling of the meal segmentation of opaque filled loops and flocculation of barium

Neurodigestive Asthenia Gastroenterologic Analogy to Neurocirculatory Asthenia Z Maratka[6] (Charles Univ Prague) describes neurodigestive asthenia as a condition of poor health with gastrointestinal symptoms and delicacy sen

TABLE 1—SYMPTOMS AND SIGNS OF AUTONOMIC LABILITY

	%
Weakness	78
Headache	75
Sweating	46
Dysmenorrhea	32
Mydriasis	50
Dermographism	25
Exophthalmus	4
Basal metabolic rate over + 20% ...	17
Abnormal vegetative reflexes	57
Solar syndrome	91

[illegible] tachy [illegible] p to + 20/min [illegible] — 8/m [illegible]

sitiveness and lowered efficiency of the digestive tract but no organic lesion It affects young persons with predominantly asthenic body build symptoms and signs of autonomic lability and more or less distinct psychoneurosis

In 50 patients the most common complaints were epigastric discomfort a sense of fulness after meals belching nausea indigestion after eating large meals irregular bowel

(6) G [illegible] 75 2 8 237 1949 50



F g 10 (top left).—O e mo th afte v gotomy Note st ik g dil tat on f duod num St ma h sh ws good tone

F g 103 (t p ght).—S m th aft v g tomy Small t st l j tte n t ll d tu bed w th ab rm l s gm t t n f loop nd flocul t on f b m Head f m l b n t y t hed c cum fte fou h u No r ry of g str to and m t l ty

F g 104 (bott m l ft).—On w k ft gotomy S b g t c r t nt on D latat n of duodenum and d lay d mot l ty f small test e

F g 105 (b ttom ght).—S month aft r got my Stom h mpty Head of meal in spl n fl u Sl ght gmentat on of b m filled loop till e dent

(Courte y of Isa c F *et al* Am J Roe tg l 63 66 75 J u ry 1950.)

The patient is most often an unmarried woman aged 18 25 who is emaciated and has a repugnance to food usually associated with amenorrhea and constipation Examination reveals severe cachexia dry hypertrichotic and occasionally scaling skin and cold extremities Bradycardia hypothermia and hypotension are found Cheilitis glossitis gingivitis and dental decay are common Laboratory studies are normal except for low basal metabolic rates of — 20 40 per cent flat glucose tolerance curves and abnormal electroencephalograms The patient is indefatigable and active out of proportion to her malnutrition

Simmond s disease presenting a similar clinical picture can be readily differentiated It occurs in middle aged women and is precipitated by physical illness Weight loss is at first minimal later profound and dramatic There are premature aging wrinkled skin loss of pubic and axillary hair loss of sexual desire and atrophy of sex organs lassitude and weakness low basal metabolic rate and a disturbed glucose tolerance curve Amenorrhea is present in only one half of the cases

In psychologic development the child who later develops anorexia nervosa is a good fanciful little girl with vivid imagination She is lonely and seclusive fits poorly into the family pattern and does not make friends easily She is usually the product of unstable parents with a food fetish and eating habits are under close observation She is chubby intelligent energetic and obedient in preadolescence With onset of the menarche she becomes irritable and aloof and has conflicts with her parents particularly the mother but remains dependent on the family When teased about her weight she responds with severe dieting despite a healthy appetite Anorexia comes later She becomes busy ambitious extremely conscientious and feels pushed to perfection in decorum and scholarship She obviously feels insecure

Tense hyperactive alert and rigid she walks talks and thinks rigidly She becomes a puritanical old maid introverted serious and obstinate beyond reason If married there is unsatisfactory sexual adjustment with repugnance for coitus She is moody and feels she is unwanted and a failure

The patient defends herself against the menace of society and family by rejecting food Persistent imperative recur

movements constipation diarrhea and other dyspeptic symp toms Almost all patients had cardiovascular symptoms Signs of autonomic imbalance (Table 1) were frequent

The first manifestations of this condition may be traced to childhood Puberty is critical for the onset of overt symp toms After 40 the symptoms tend to decrease or disappear One of the main characteristics is the variability of symptoms over the years

Differential diagnosis should include organic diseases of individual digestive organs and psychoneurosis with gastro

TABLE 2—DATA IN DIFFERENTIAL DIAGNOSIS OF NEURODIGESTIVE ASTHENIA AND PSYCHONEUROSIS

	Neuro igestive As henia	Psycho eu osis
Constitution	Asthenic	Variable
Onset	Near puberty	Any time
Symptomatology	Less variable	More variable
Duration of symptoms	Chronic	Intermittent or chronic
Dependability on diet	Important	Not important
Digestion previously	Poor	Cood
Cardiovascular symptoms	Almost always	Often
Emotional influence	Considerable	Definite
Effect of psychotherapy	Improvement	Sometimes cure

intestinal symptoms Table 2 presents data which may aid in differentiation of the latter from neurodigestive asthenia

Etiologic factors important in genesis of neurodigestive asthenia are heredity and psychogenesis Prognosis for life is good but prognosis for cure is poor Therapeutic measures include a hygienic way of living and reassurance

[Various writers have called attention to this group of patients al though they did not make the clearcut distinctions between them and the neuro with nonorganic digestive disturbances—who may be fat lean or hypersthenic Most authorities will agree that the author s conception is a distinction with a difference —Ed.]

Compulsion Neurosis with Cachexia (Anorexia Nervosa) This peculiar form of disease fully described in the last cen tury as anorexia nervosa vividly illustrates the interrela tionship between emotions and body functions it is believed to be primarily a psychologic and secondarily a physiologic disturbance Franklin S DuBois[7] (New Canaan Conn) de scribes the nature of the personality or psychologic disorder and the psychiatric category in which this disease is placed as fundamentally a compulsion neurosis with the major symptom cachexia

(7) Am J Psych at 106 107 115 A gust 1949

little known Clinical phenomena of the disorder are similar to those of ulcer Roentgen examination is decisive in diag nosis since it demonstrates the typical forms of the prolapse which can be classified into three groups

In group 1 a small mucosal fold has prolapsed into the pyloric canal This form is relatively frequent On roentgen examination the outgoing peristaltic wave makes this fold apparently disappear In group 2 the longitudinally placed mucosal fold in the pyloric canal extends its free end into the duodenal bulb in the form of a mushroom like filling de fect when slight compression is exerted on the bulb filled with contrast substance This is a unilateral partial prolapse the frontal view of which is the picture just described while the profile view shows a unilateral dent in base of the bulb so that the length of the pyloric ring on this side seems to have increased Group 3 includes total or circular prolapse in which the parapyloric impression of the base of the bulb is strongly accentuated so that the pyloric canal appears lengthened and a thickening of the pyloric muscle ring is simulated as in pyloric hypertrophy The distance between the gastric outlet and the base of the bulb is considerable

When the clinical disturbances are slight treatment may first be conservative (diet bed rest drugs) Indications for operation are pronounced bleeding tendency symptoms of stenosis and attacks of pain which resist treatment Mucosal prolapse should be accepted on the strength of positive clini cal and roentgen signs even in cases in which palpation and inspection of the specimen during and after operation do not reveal any gross changes and in which macroscopically there is only gastritis Absence of gross anatomic changes raises the suspicion of prolapse and many negative operative results with positive roentgen findings represent unrecognized mu cosal prolapses Verification of atypical mobility of the mu cosa on the muscularis should never be overlooked

Prolapse of Gastric Mucosa and Its Possible Relationship with Peptic Ulcer and Upper Gastrointestinal Hemorrhage S P Bralow G H Becker S Scheinberg and H Necheles* (Michael Reese Hosp) report three cases in which prolapse of gastric mucosa was associated with duodenal ulcer and two in which severe upper gastrointestinal hemorrhage was asso

(9) Am. J Dig t. D s. 17 65 69 M h 1950

rent thoughts of food fit the pattern of obsession just as repeated unreasonable imperative rejection of food conforms to the pattern of compulsive action These components combined with obvious tension formulate the obsessive compulsive ruminative tension state ending in cachexia

Constitutional predisposition is only one factor in this disorder Inanition prevents maturation and the assumption of adult responsibilities and causes suppression and rejection of sexual desire and menses It is also suggested that rejection of food is a device to atone for guilt of ambivalent reactions to parents Food rejection and inanition are rewarded by solicitude and indulgence enabling the patient to regress to infantile reactions Some behavior changes including deviations in thought result from ill nourished organs

Many mild cases probably recover spontaneously as time brings maturity and the severance of parental ties When the disorder is fully developed the possibility of satisfactory treatment is remote and permanent recovery is improbable Although 5 of 10 patients treated by DuBois made limited adjustments all remained introspective and stubborn and 4 continued to have difficulty in relations with the opposite sex

Recommended treatment consists of psycho and somato therapy Hospital or sanatorium care is essential with bed rest and semiambulation prescribed initially Six modest feedings totaling 1 500 calories/day are supplemented with vitamins intramuscular injections of liver extract and high fluid intake Mild cathartics are given Repeated reassurance is necessary to explain the initial uncomfortable symptoms such as gastric distention and cramps In two or three weeks food intake is increased to 3 000 3 500 calories/day Insulin in tonic doses of 5 25 units before meals enhances ability to accept the added food Exercise and occupational therapy are introduced Little reference is made to food and diet reassurance and explanations are stressed and mental hygiene re educa tion attempted Active therapy lasts three months with a follow up of three years desirable

Clinical and Roentgen Study of Prolapse of Gastric Mucosa into Pylorus and Duodenal Bulb According to E A Zimmer[8] (Fribourg) the fact that this type of prolapse is relatively common and hence of practical significance is still too

(8) Schw r med. W b s h 80 351 358 Apr 8 1950

ciated with x ray evidence of prolapsed gastric mucosa Case I is given here

Man 39 had a typical history of ulcer dating back 12 years For six months before admission the gnawing burning pain experienced by the patient was almost constant and was intractable to rigid medication An x ray revealed a moderate degree of prolapse of the gastric mucosa with spasm of the second portion of the duodenum (Fig 106) Operation disclosed prolapse of the prepyloric mucosa and a posterior penetrating ulcer in the second portion of the duodenum involving the head of the pancreas Figure 107 reveals the relation of ulcer to prolapse

On the basis of these and other cases the authors propose the following etiologic sequence of events leading to prolapse of gastric mucosa into the duodenum peptic ulcer gastritis hypertrophied rugal folds and eventual prolapse The original ulcer may heal but once prolapse has occurred it may recur The most frequent symptoms are vague epigastric distress with intermittent cramping bloating and a sense of fulness after meals Nausea and vomiting occasionally occur These manifestations are compatible with a variable degree of pyloric obstruction In many cases prolapse will respond to conservative management and operation is indicated only in cases of severe intractable pain persistent pyloric obstruction or repeated massive hemorrhage

[Although ome roentgenolog sts are doubt g Thom ses concerning this condition the numerous current contributions on the subject at home and abroad are reminders of the old saw where there is smoke there is fire —Ed]

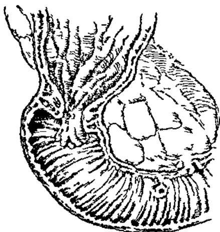
Chronic Gastritis J hn W Findley Jr Joseph B Kirsner Walter Lincoln Palmer and Theodore N Pullman[1] (Univ of Chicago) made a comparative analysis to determine the symptomatology and the gastric secretory response to histamine in chronic gastritis Three groups of patients 50 of whom showed atrophy of the gastric mucosa 50 superficial gastritis and 50 hypertrophic gastritis and a control group of 100 persons with apparently *normal gastric mucosa* were *studied* So far as possible other organic disease was ruled out

The predominant complaint of the patients abdominal pain was located most often in the epigastrium and showed little variation in incidence or time of occurrence Other symptoms likewise did not differ significantly among the groups

(1) Am J M d 7 198 06 A gu t 1949



Fg 106—F'lm show ng prolapse f g stric mucosa and spasm of duod um (Court sy of Br low " P et l Am J D g t D 17 65 69 Ma ch 1950)



Fg 107—Su g cal spec m sh w g r lat n of d len l ulc r to p ol psed g t ic mu osa (Co t y of Br l w S P el l An J D g t D s 17 65 69 M rch 1950)

acid (histamine) is lowest in patients with mucosal atrophy (3) Some individuals with superficial gastritis are capable of producing large amounts of acid but the mean histamine se cretion is less than it is in persons with hypertrophic gastritis or in controls The incidence of anacidity in superficial gas tritis is second only to that in atrophy (4) The incidence of histamine anacidity seems greater in patients with hyper trophic gastritis than in persons with normal mucosa but

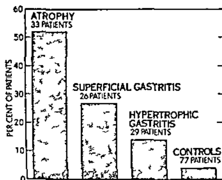


Fig 109 —I dence f h tamin id ty (Courtesy of F ndley J W J *et al* Am. J Med. 7 198 206 A gu t 1949)

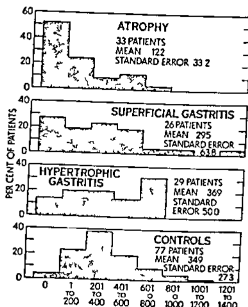
the mean acid secretion is approximately the same This may be due to the fact that a certain proportion of individuals with hypertrophic gastritis secrete excessive amounts of acid

New Diagnostic Criterion for Gastric Syphilis is presented by Herbert Berger[2] (Staten Island N Y) who reports two illustrative cases Gastric syphilis can be diagnosed only when the patient has untreated tertiary syphilis demonstrable x ray defect and gastric symptoms The symptoms and x ray ap pearance must not improve under conventional therapy but should respond strikingly to specific antisyphilitic therapy In the past antisyphilitic therapy has been carried out with arsenicals and bismuth but in the cases reported response oc curred after treatment by the rapid method with penicillin The advantage of the rapid method is that results of treat ment are obtainable within one or two weeks Since this in terval is not greater than that usually required for preparation

(2) G t oe t l gy 14 147 151 J ry 1950

Distress when present and distinct from pain showed no characteristic pattern

The gastric secretory response to histamine was deter mined quantitatively in 165 patients by measuring total milli grams of free HCl total volume and the average units of free acid secreted during the hour following subcutaneous injec



F g 108 —D t b t n of total m ll g ms of HCl ecret d d g e hour ft je tion of h tam (Cou t y of F ndl y J W Jr., e t l Am J M d 7 193 206 A gu t 1949)

tion of histamine Patients with mucosal atrophy secreted the smallest amounts of acid and those with superficial gastritis the next smallest although two of the latter group secreted large amounts of acid The distribution is given in Figure 108

The incidence of histamine anacidity is presented in Figure 109 Significant statistical differences were found between the atrophy and control groups and between the superficial gas tritis and control groups

The conclusions drawn from the study were (1) The common types of chronic gastritis apparently produce no symptoms (2) Histamine anacidity occurs most frequently with atrophy of the gastric mucosa The mean secretion of

and 23 vagotomy patients 7 days to 45 months after operation

Chloride minute output was for normal persons 0 24 m Eq /minute for ulcer patients 0 41 m Eq /minute and for vagotomized patients 0 18 m Eq /minute The chloride minute output illustrates wide fluctuations in gastric secretory activity Secretion is lost through the pylorus at the rate of 6 0

$V_1 + V \quad V_2 + V_3$

Fg 110—D g m f st m h w th Le n t b pl l st at g t f tt f l m m a r d d cal l t d by the dy d l ti tech V_1 (o) m l j ted — 100 sot n c sal e co t g 7 mg /L ph ol red) a d V_2 (vol m a p t d 10 m utes fter i je tion) are m s r d d ctly wh l V_3 (pyl effl) and V_4 (ga t se t n) e alcul t d a s d cated t t (Cou t y f B k J R t al S g Gyn c & Ob t 90 155 170 F b ry 1950)

cc /minute in normal persons and ulcer patients but following vagotomy the rate drops to 3 5 cc /minute Regurgitation of duodenal contents into the stomach is more common in vagotomized ulcer patients than in normal persons or ulcer patients There was no change in the reduction of chloride minute output following vagotomy when tests were conducted over an extended period

Introduction of 100 cc perfusate containing either 300 or 750 mg acetylcholine into the stomach produced a consistent statistically significant secretory rate in normal persons ulcer

of patients with gastric conditions for operation no time is wasted if the gastric lesion is not due to syphilis

[Occasionally there may be symptomatic improvement during or following antisyphilitic treatment of patients with nonsyphilitic gastroduodenal lesions but objective (anatomic) changes are nil Penicillin therapy represents a distinct advance In my experience fewer patients are now seen harboring late specific abdominal visceral lesions The same appears true of cardiovascular lesions Clawson (Minnesota Med *33* 437 440 *May 1950) called attention to this decline In the five years 1914-18 the* incidence of death due to syphilitic heart disease was 17 4/1 000 autopsies It was 2 3/1 000 during the four years 1944 47 One can only speculate as to the cause of this great decline but it is reasonable to presume that improved medical education earlier diagnosis and improved methods of treatment play a considerable role —Ed]

Chloride Output Rate of Human Stomach in Healthy Subjects and Ulcer Patients, Effects of Vagotomy and Acetylcholine Studies by Dye Dilution Technic are reported by John R Brooks John M Erskine Thomas Gephart Oliva Swaim and Francis D Moore[3] (Harvard Univ) Most studies of gastric secretion have been confined to titration of free and total acidity neglecting the pepsin mucin total base and *potassium content Since the acid in gastric secretion is partly* neutralized by base secreted in the antrum or by reflux of the alkaline duodenal fluid titratable acidity is but a secondary reflection of total acid secretion These errors are compounded when titratable acidity is multiplied by volume units to yield milliequivalents of hydrochloric acid

Gastric secretion was investigated by the dye dilution method which depends on the introduction of a measured quantity of dye into the stomach and its aspiration 10 minutes later with the gastric juice accumulated during that period From the dilution and total quantity of dye recovered total secretion of the stomach may be calculated as well as that portion of the gastric juice *lost through the pylorus* (Fig 110) Analysis of aspirated gastric juice for total chloride content permits expression of gastric secretory rate predominantly traceable to parietal cell activity Results are in terms of total chloride secretion of the whole glandular cell mass/unit of time the chloride minute output Data on total gastric secretory activity in the human patient which are otherwise not available can be obtained in a few hours *Studies* were made on 37 normal adults 29 patients with duodenal ulcer 20 of whom were intractable to medical therapy

(3) S g Gy ec & Ob t 90 155 170 F l ry 1950

The evidence suggests that gastric and duodenal ulcers are diseases of different pathogenesis The concept that duodenal ulcer is caused by the action of abnormal degrees of acidity over abnormally long periods is supported by the evidence Observations indicate however that gastric ulcers are not attributable to this cause

[These differences in the ga tric secretory milieu of patients with duodenal ulcer and gastric ulcer largely confirm findings of previous investigators For example Dragstedt Camp and Fritz (Ann Surg 130 843 856 October 1949) pointed out that in patients with gastric ulcer acid secretion is the same or less than in normal people The increased nocturnal secretion in patients with duodenal ulcer which may be three to four times the amount in normal persons is attributed to the neurogenic factor hence the significance of excess acid pepsin in pathogenesis With respect to etiology they believe that gastric ulcer is due to a decrease in resistance on the part of the gastric wall and not to any corrosive properties of the gastric content —Ed]

Nocturnal Gastric Secretion in Patients with Benign Gastric Ulcer Erwin Levin Joseph B Kirsner and Walter Lincoln Palmer[5] (Univ of Chicago) compare the periodicity and variability of nocturnal gastric secretion in patients with benign gastric ulcer normal subjects and patients with duodenal ulcer There appeared to be no significant difference in total volume in patients with gastric ulcer and normal individuals but that in patients with duodenal ulcer was significantly greater than in gastric ulcer patients In all three groups night secretion of gastric juice was continuous with a tendency for the average hourly volume to decrease gradually during the night Although individual variations existed in all groups the secretory rate remained at a consistently higher level in the duodenal ulcer patient

The total amount of acid and concentration of free hydrochloric acid secreted during the night was lowest in gastric ulcer patients Secretion of hydrochloric acid was continuous only in duodenal ulcer patients Although there were individual fluctuations in amount and concentration of free acid usually there was a constancy on successive nights in the same individual Average hourly concentration was highest in patients with duodenal ulcers and lowest in gastric ulcer patients and both groups showed a gradual decrease during the night There appeared to be no correlation between the degree of gastritis determined gastroscopically and the amount of acid produced

(5) A I t M d 30 1020 1032 M y 1949

and vagotomized patients Although the secretory rate in creased in response to the drug degree of response among the three groups was not significantly different Only normal pa tients showed a significant increase in chloride concentration due to acetylcholine despite the change in rate of chloride minute output in all No group revealed a significant change in pH Similar secretory responses were produced by hista mine and insulin hypoglycemia Local application of acetyl choline reduced the evacuation rate in all groups and increased the frequency of duodenal regurgitation in vagotomized pa tients The local effect of acetylcholine is due to its particular organic configuration and is not a nonspecific effect of its chemical constituents

Role of Gastric Acidity in Pathogenesis of Peptic Ulcer A H James and G W Pickering[4] (St Mary s Hosp London) maintained continuous aspiration of gastric contents for 24 hours in 20 patients with duodenal ulcer 23 with gas tric ulcer and 20 controls Acid content of the aspirate was *determined at frequent intervals Although the mean value for* maximal acidity in duodenal ulcer patients was 83 1 m Eq /L. and was greater than for the normal subject the difference was not statistically significant The mean minimal acidity during aspiration was more than normal and duration of acid ities greater than pH 2 was increased These increases were statistically significant Acidity rarely fell below pH 5 5 in either controls or those with duodenal ulcer Curves of intra gastric acidity showed that in patients with duodenal ulcer as contrasted with controls there was a higher level of acid ity and less conspicuous neutralization after eating and that higher acidities were maintained at night after food had dis appeared from the stomach

In patients with gastric ulcer the mean value for maximal acidity (53 5 m Eq /L) was less than normal but the differ ence was not statistically significant Duration of acidities greater than pH 2 was normal and of acidities less than 5 5 was increased significantly In about two thirds of those with gastric ulcer intragastric acidity curves fell almost to neu trality during that part of the night when the stomach was empty This gastric neutralization is apparently due to cessa tion of acid secretion

(4) Cl n. Sc. 8 181 210 S ptembe 1949

medical histories were obtained on 85 of the original group Follow up questionnaires showed no history of dyspepsia in 45 history of minor dyspepsia in 21 history of dyspepsia not suggestive of ulcer in 9 and history of dyspepsia suggestive of ulcer in 10

Results of the original test meal showed that the highest free acidity obtained was practically the same in all groups The average volume of juice secreted by those in whom symptoms suggestive of ulcer subsequently developed was significantly greater than that secreted by the others All dyspepsia suggestive of ulcer occurred in those who had secreted more than 100 ml gastric juice an hour (Fig 111)

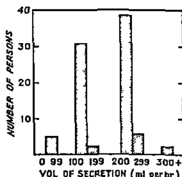


Fig 111 —V l m f g t) d d l pm t of b q t mp tom b t b d l m dy p [k g t g pept l t ppl d l m th dy p p (C t y f D ll R t l L t 2 984 985 N 6 1949)

Results indicate that hypersecretion is a cause rather than an effect of peptic ulcer

Nitrogen Balance Studies in Chronic Peptic Ulcer Disease To determine the value of high protein feedings or hyper alimentation regimens in peptic ulcer Thomas S Sappington and Henry L Bockus[8] (Univ of Pennsylvania) studied pro tein requirements of five patients with chronic uncomplicated ulcer Utilizing an hourly milk feeding program they con ducted nitrogen balance studies and routine blood studies All were on suboptimal protein diets before hospitalization and one had low serum proteins Anemia was not found in any

One patient demonstrated a consistently positive nitrogen balance and was considered to have had a previous nitrogen deficiency therefore an increased protein requirement was in dicated Another patient gave evidence of previous nitrogen deficit and hence increased protein requirement despite incon clusive nitrogen balance data A third patient probably had

(8) A I t M d 31 271 81 Augu t 1949

Hydrochloric Acid Test in Diagnosis of Ulcer Geor. Gottsegen and Bela Hermann[6] (Budapest) studied the effect of hydrochloric acid and compared the reactions of normal patients and those with ulcers by the following procedure

METHOD—Sixty minutes after a test breakfast the stomach was emptied completely and sodium bicarbonate given through the tube Gastric contents were again removed after 20 minutes and hydro chloric acid was given Reactions were closely observed and to pre vent habitual reactions the drugs were sometimes given in reverse order If pain was caused by the acid the reaction was considered positive

Four hundred patients with normal gastrointestinal tracts were tested first only four of them reacted positively and these exceptions were found to have ulcer craters by x ray In gastric cancer four of six tests gave negative results in the two positive cases there may have been superficial ulcera tion of the neoplasm at the time but this could not be deter mined When the test was given to peptic ulcer patients re actions were positive in one half of the patients with gastric one third with duodenal and all with jejunal ulcers

Subjective objective clinical and roentgenologic findings were studied in an effort to find why there was such a diver gence in ulcer bearing patients X ray findings gastric secre tion length of disease severity of pain and presence of occult bleeding failed to explain the difference in reaction to hydro chloric acid

It seemed significant that when a remission in symptoms occurred the reaction changed from positive to negative suggesting that it was the acute ulcer which reacted with pain In the development of ulcer there is probably a period when there is a tendency to healing and reparative processes occur At such times the base of the ulcer is protected by granula tions and the acid does not produce pain though the anatomic changes persist

It is believed that the hydrochloric test may be an aid in evaluating progress of therapy in peptic ulcers

Gastric Secretion and Subsequent Dyspepsia Follow up Study on 100 normal medical students subjected to histamine test meals 15 years ago was attempted by Richard Doll F Avery Jones and N F Maclagan[7] (London) Subsequent

(6) Ga t oe t log 74 70 79 1948 49
(7) La c t 2 984 985 No 6 1949

symptomatology and difficulty in localizing the lesion However Smedal states that accurate anatomic diagnosis is possible with the roentgenographic triad which usually indicates ulcer in the sphincter or on its duodenal slope deformity of *the base of the cap a poorly differentiated* sphincter and antral spasm Figure 112 shows the location of ulcer in the pyloric ring

George A Boylston[1] (Univ of *Oregon*) analyzed *20* such cases with adequate follow up In 15 ulcer of the ring was

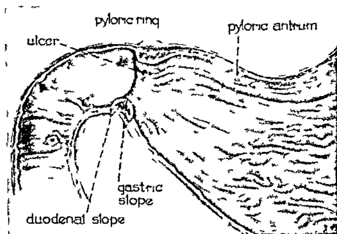


Fig 112 —Pyl g h w g typ l lo t f l (Court y f B yl to G A A h I t M d 84 53 539 O t b 1949)

demonstrated at operation in 5 by x ray alone Prolonged follow up and/or biopsy of each lesion revealed only one malignant ulcer The symptoms averaging 6½ years in duration were typical of peptic ulcer in 11 patients Complaints included gaseous distress after eating in 7 nausea in 10 intermittent obstructive symptoms in 4 and crisis like pain and vomiting in 1 There was no cicatricial pyloric stricture X ray study localized the ulcer in the ring in 12 cases in 5 others craters localized close to but not in the ring on x ray proved at operation to be in the ring Fluoroscopic examination showed antral spasm in eight cases spasm of the bulb in seven and four hour retention of barium in two Of 15 pa

(1) A h I M d 84 53 539 O t be 1949

protein deficiency demonstrating low urinary nitrogen values Others had *no protein deficiency as shown by normal* nitrogen balance

These results suggest that a daily minimal intake of 15 Gm nitrogen be used for uncomplicated peptic ulcer This is approximately equivalent to 95 Gm protein An hourly 4 oz milk diet is inadequate to meet this protein requirement therefore extra whole protein should be added when the diet is restricted to milk This supplement is easily available in the form of skim milk powder or calcium caseinate

***Gastroscopic Appearance of Gastric Mucosa in Peptic* Ulcer** Recent studies have demonstrated significant differences in the maximal free acidity of gastric secretion between patients with gastric and with duodenal ulcer Maximal free acidity after administration of histamine was low in 21 per cent of the gastric ulcer group it always exceeded 50 clinical units in the duodenal ulcer group William E Ricketts Joseph B Kirsner and Walter L Palmer[9] (Univ of Chicago) studied two consecutive series of patients with duodenal and gastric ulcer *respectively to compare the gastric acidity* and gastroscopic findings and to seek a possible explanation for the pronounced differences in gastric secretion between the two groups Gastric acidity was measured by the histamine test (0 1 mg/10 kg body weight) Gastroscopic findings were classified as (1) normal (2) atrophy (atrophic gastritis) (3) an irregular cobblestone like mucosa (hypertrophic gastritis) and (4) edema hyperemia and adherent exudate (superficial gastritis)

Analysis demonstrated that peptic ulcer may occur with any type of gastric mucosa the only essential is presence of free hydrochloric acid However there is considerable difference in the appearance of gastric mucosa in gastric and in duodenal ulcer Incidence of atrophy of gastric mucosa is higher in gastric (20 per cent) than in duodenal ulcer (5 per cent) Incidence of hyperplastic mucosa is higher in duodenal (41 per cent) than in gastric ulcer (19 per cent) The frequency of atrophic and inflammatory changes of gastric mucosa in gastric ulcer accounts in most cases for the low output of acid

Ulcer of Pyloric Ring Report of 20 Cases *This condition* presents a diagnostic problem largely because of a variable

(9) Am J M Sc 217 54 544 May 1949

tients Reasons suggested for the increase included greater use of x rays and an increased tendency to hospitalize ulcer patients particularly as the food situation grew worse Increasing psychic stress inadequate nutrition and growing consumption of tobacco were probably more active as contributory causes of ulcer in men than in women

During 1912 28 a period previously reviewed by Semb the ratio of perforations in men to those in women was 4 1 From 1929 to 1945 it was 11 1 During these same periods however there was little change in the influence of ulcer location on the tendency to perforation Average age of patients with perforations gradually increased with women showing the greater increase This as well as the increase in age of patients without perforation paralleled the increasing age of the general population of Oslo except that the average for women with perforations was higher than that of the general population Bjørn Hansen states however that increased ulcer incidence in older age groups is real it is not due to chronic or protracted ulcers and readmissions The decrease in younger age groups may result from improved living standards for domestic workers higher wages shorter working hours regular meals and improved oral hygiene

Localized Sealed off Perforation in Recurrent Duodenal Ulcer Maurice Feldman[3] (Univ of Maryland) discusses a medical type of sealed off spontaneous pinpoint perforation generally associated with a recurrent active duodenal ulcer with a demonstrable niche defect Severe symptoms and shock are absent Patients are usually ambulatory and there is no free air in the peritoneal cavity Clinical history is characterized by mild and transient attacks not relieved by ordinary treatment methods The patient often complains of persistent pain in the epigastrium somewhat to the right of the midline It lasts longer than usual and tends to become milder and intermittent Later there are persistent soreness and discomfort in the epigastrium sometimes increased by food Vomiting often occurs during the episode X ray examination reveals a small gas bubble in the subhepatic area above and outside of the duodenal contour Occasionally a small amount of fluid capped with air is seen in the base of the pocket In Feldman s series of five cases no barium entered the pocket

(3) Am J M S 218 378 383 Octobe 1949

tients treated surgically only five reported dyspepsia post operatively On medical management three patients had good results and two had recurrence of symptoms on interrupting therapy

Review of this series and reported cases shows that malig nant ulcer within the pyloric ring is rare However since no significant symptom complex characterizes these lesions x ray and fluoroscopic examinations are diagnostically important

Investigations of Alterations in Ulcer Clientele in Oslo Municipal Hospital, Ullevaal, over Period 1916-45 Haakon Bjørn Hansen[2] analyzed all cases of peptic ulcer on the medi cal service of this hospital from 1916 to 1941 and with Carl Semb surveyed all cases of perforated peptic ulcer Particu lar attention was paid to the years 1916-25 1935 36 and 1940 41 Average age ratio of men to women was 38 35 years in 1916 25 and 40 47 in 1935 36 and in 1940-41 In men hemor rhage decreased from 74 per cent (75 per cent in women) in 1925 26 of which 60 per cent was gross to 35 per cent (39 per cent in women) in 1935 36 and 1940 41 of which prac tically all was gross There was an increase in the incidence of melena over that of hematemesis coincident with a change in ulcer location from the body of the stomach toward the pylorus and duodenum Average age at the first hemorrhage increased from 38 to 42 years for men and from 35 to 50 for women In both men and women symptoms tended to be of longer duration on both first and readmissions during 1935 36 and 1940-41 than during 1916 25

During 1916-25 x ray studies were made of only 40 per cent of the patients usually at the end of treatment owing to the frequent presence of hemorrhage X rays showed the ratio of duodenal to gastric ulcer in men to be 1 1 and in women 1 1 7 In later years x rays were made before admis sion on practically all patients Thus this ratio for men and women changed to 5 1 and 1 1 in 1935 36 and 1 3 1 and 1 1 7 in 1940-41 The number of men with ulcer and the per cent of total admissions increased greatly the latter from 3 1 per cent in 1915 16 to 10 8 per cent in 1940-41 The increase for women was from 3 per cent to 4.3 per cent over the same period Thereafter an abrupt decline occurred because limited hospital facilities permitted acceptance of fewer ulcer pa

(2) Act med S d 135 149 171 1949

gestion was obtained In 64 per cent this conformed to a typical ulcer pattern and in 68 per cent symptoms had persisted longer than one year Onset of perforation seemed unrelated to eating habits drinking or smoking or to a particular phase of digestion The moment of perforation was not correlated with position of the patient straining or physical activities The number of perforations occurring in autumn months was considerably lower than in any other season Though there was no significant daily variation in incidence perforation was nearly twice as common in the afternoon and evening as in the morning During the three days before perforation 28 per cent of the patients had no gastric symptoms 37 per cent complained of intermittent abdominal pain 22 per cent of constant pain and 13 per cent had vague complaints such as nausea heartburn and a sense of fulness A physician would in most cases have been unable to anticipate the approaching disaster since no specific pattern of symptoms seemed to lead to perforation

In men perforation of duodenal ulcer was four times as common as perforation of gastric ulcer In women perforation of gastric ulcer occurred twice as often as perforation of duodenal ulcer

[This is an instructive contribution to our knowledge of the most lethal complication of ulcer Of interest is the absence of those factors traditionally regarded as provocative of perforation as well as its unpredictability —Ed.]

Gastric Perforation Clinicopathologic Study John G Shellito and Andrew B Rivers[5] (Mayo Clinic) studied 195 cases of gastric perforation 101 due to benign and 94 to malignant lesions to discover differences which would facilitate a preoperative diagnosis The average age of patients in both groups was 52 7 years the ratio of males to females was 6 8 1 in cases of perforated benign ulcers and 3 9 1 in malignant perforations Free acute perforations occurred in only 4 3 per cent of malignant lesions and in 5 9 per cent of benign the greatest number in this series were walled off and well localized by natural peritoneal barriers

A typical ulcer history was obtained in 61 4 per cent of patients with perforated benign lesions but in only 28 6 per cent with malignant perforations An atypical but suggestive

(5) G st oe t logy 12 919 933 J 1949

Because of the minimal amount of air which escapes from the pinpoint perforation the subhepatic gas bubble is best demon strated by the spot film compression technic with the patient in an erect position (Figs 113 and 114) This small amount of air and sometimes fluid usually disappears within a few weeks of treatment

This form of walled off perforation probably occurs more often than has been suspected It should be looked for in all



F g 113 (left) —F lm made n t p s t on with sp t film comp e on sh w ing m k dly d f m d duod l bulb w th la ge a r b bble bo e d odenum (rows) N te fl ttened ba f pock t d to mall mo t of fl d

F g 114 (ght) —S me c s F lm mad n re mbent prone po t n w thout comp on N g pock t b d mo trat d

(Courtesy of Feldman M Am J M S 218 378 383 O tob 1949)

ambulatory patients with recurrent duodenal ulcer who pre sent symptoms which are more severe than those usually experienced

Factors Associated with Perforation in Peptic Ulcer have been studied by Christopher Strang and I O B Spencer[4] (Newcastle upon Tyne) Of the 189 patients with perforated peptic ulcer reviewed all but 12 were men giving a much greater male to female ratio than is generally true for peptic ulcer Perforation is rare under age 20 but has a fairly even distribution in other decades Jobs entailing a moderate amount of responsibility were held by 18 5 per cent of the ulcer patients whereas only 5 per cent of the hospital popula tion held employment with a similar amount of responsibility

In 91 per cent of the patients a history of previous indi

(4) B t M J 1 873 876 Ap 15 1950

in the individual patient pathologic examination of the lesion is the only certain procedure

[The profession is indebted to the late Andrew B Rivers for his several investigations with respect to pain and its characteristics in primary anastomotic and recurrent postoperative ulcer The significance of its location the radiation character probable nerve pathways and differential features of visceral and somatic elements are problems which he helped so much to clarify His description of the symptom complex of duodenal ulcer perforating into the pancreas is a classic (1948 YEAR BOOK OF GENERAL MEDICINE p 665) —Ed]

Management of Patients with Bleeding from Upper Gastrointestinal Tract with Buffer and Thrombin Solution Byrne M Daly Charles G Johnston and Grover C Penberthy[6] (Wayne Univ) developed the buffer and thrombin method during study of 100 consecutive cases and report the procedure found most effective

METHOD —A Levin tube passed through the nose into the stomach is washed out with buffer or saline solution and 50 cc of M/7 phosphate buffer then introduced into the stomach and left five minutes An additional 50 cc phosphate buffer is introduced and with it 10 000 units of topical thrombin The tube is clamped 30 minutes during which blood studies are made and if blood loss appears serious a transfusion is given After 30 minutes the clamp is removed from the tube and slow gentle suction is applied by mean of a pump with a valve mechanism that permits low suction not to exceed 1 ft water The material removed is observed through a glass connector If bleeding has stopped the material usually is finely granular and light colored if bleeding continues fresh blood stained material can be seen in the tube If there is no ble ding 50 cc buffer solution is introduced every half hour allowed to remain a half hour and then aspirated The buffer may be given by slow drip This process is carried on for several days If bleeding continues the process is repeated If the bleeding appears uncontrolled by thrombin administration other measures mu t be resorted to The phosphate buffer is made by mixing 20 4 Gm disodium phosphate in 1 L water with 1 95 Gm dihydrogen potassium phosphate in 100 cc water pH is 7 6

Bleeding in 87 patients was controlled by use of thrombin buffer alone In eight others the hemorrhage was controlled but recurred in three it could again be controlled but for five operation seemed the safer procedure In four patients bleeding recurred after having been controlled with thrombin and further treatment was ineffective One other patient died of massive hemorrhage in which bleeding was at no time controlled

Though the thrombin and buffer method i useful in con

(6) A n. S g 129 832 839 J 1949

story was given by 23 8 per cent of patients with benign and 36 2 per cent with carcinomatous perforation and a history not typical of ulcer was obtained from 13 8 per cent of patients with benign lesions and 24 5 per cent with malignancies Slow insidious onset of symptoms was the rule with perforation causing exaggeration of symptoms Perforation of benign ulcers seemed to be associated with more definite symptoms whereas malignant lesions progressed faster All acute perforations gave a somewhat typical history of pre existing ulcer A mass was palpable in only 25 5 per cent of malignant lesions this finding should indicate that the lesion is malignant and rather far advanced Weight loss usually considered of prime importance in diagnosis of malignant lesions occurred here more often in benign lesions Hypoacidity tended to occur in malignant perforations and hyperacidity in benign although normal gastric acidity was often found in both groups A rigid abdomen was found only in patients with acute perforations

Most gastric perforations occurred on the posterior wall of the lesser curvature Carcinomatous lesions tended to locate toward the pylorus and benign lesions near the angle Location of the lesion on the anterior wall and greater curvature is not considered a specific indication of malignancy Pancreatic involvement occurred in 81 per cent of benign perforations and in only 51 per cent of malignancies Carcinomatous lesions had a mean diameter of 2 52 cm compared to 1 85 cm for benign perforations suggesting that at operation lesions greater than 2 cm should be considered malignant until proved otherwise Duodenal ulcer was associated with benign gastric ulcer in 13 per cent of patients with sarcoma of the stomach in two of three instances but in no instance with adenocarcinoma In 3 per cent of benign perforating lesions an additional benign gastric lesion was found An additional malignant lesion occurred in 2 1 per cent of malignant perforations

Gastric resection is the operation of choice in walled off perforation malignant or benign as well as in free perforation In the latter case if immediate resection is not feasible primary closure followed later by gastric resection is recommended A rigid abdomen associated with gastric ulcer should be considered an indication for immediate surgery Since no significant features differentiate benign from malignant lesions

blood and to raise the red cell count above 3 500 000 Since it was impossible to foretell if a patient would require surgery to stop bleeding early operation was performed (1) on all patients over age 40 with bleeding from peptic ulcer 48 hours in duration (2) on those with appreciable recurrence and (3) on diagnosis of extensive penetration or a complicating disease Urgent operation was successfully performed in nine cases after definite diagnosis of ulcer The authors estimate that under conservative therapy mortality would have been 50 per cent of the operated group Thus an earlier and more radical surgical approach to bleeding ulcer complicated by arteriosclerosis cirrhosis portal hypertension diabetes or penetration resulted in a lower mortality

Lethality Rate of Hematemesis and Melena Treated Non operatively (Meulengracht s Regimen) and Criteria for Surgical Intervention in Bleeding Peptic Ulcer Jørgen Pedersen[8] (Copenhagen) reviewed about 850 cases of bleeding peptic ulcer and ulcer disease treated by Meulengracht s principles during a 10 year period The gross mortality rate was about 3 5 per cent in about 2 per cent death was due to exsanguination Pedersen then analyzed (1) all fatal cases of peptic ulcer hemorrhage in patients aged 40 and over (2) all cases of survivors of hematemesis or melena observed in the hospital who were over 40 had a peptic ulcer demonstrated by x ray or on operation and in whom the lowest hemoglobin was less than 80 per cent

There was no death from melena below age 60 The few patients dying from or with bleeding peptic ulcer without hematemesis were those suffering from mechanical obstructions of the stomach and duodenum In these instances the melena was considered a masked hematemesis In addition this group contained patients so debilitated they were unable to vomit the blood In patients reported to have had hematemesis before hospitalization and melena after the mortality was comparable to that for melena alone Exsanguinated patients of these two groups are considered cases for the Meulengracht regimen

Seventy per cent of all fatalities had hematemesis after hospitalization Of those dying from exsanguination 90 per cent had hematemesis in the hospital In the age group 40-49

(8) G t oe t logy 12 597 616 Ap 1 1949

trolling hemorrhage from the upper gastrointestinal tract it should not be considered a sole form of therapy When it is ineffective early operation is necessary The method in conjunction with the Patton tube is useful in determining whether a patient is bleeding from the esophagus or from below the cardia of the stomach

Combined Medical and Surgical Management of Upper Gastrointestinal Hemorrhage is the most efficient treatment according to *Thomas A Warthin Richard Warren and Egon G Wissing*[7] (Veterans Admin Hosp West Roxbury Mass) Of 86 cases of massive hemorrhage 56 (65 per cent) were due to peptic ulcer and 30 to esophageal varices gastritis or undetermined causes Among 14 cases in which no cause was found only 3 had histories suggestive of ulcer Of 11 deaths (mortality 12 8 per cent) 2 occurred in the ulcer group and 9 in the nonulcer Hemorrhage was the primary cause of death in only 6 of the 11 cases 3 died of liver failure 1 of peritonitis and malnutrition and 1 of terminal carcinoma of the stomach Ten of the 11 deaths occurred in patients who had either hepatic cirrhosis or portal hypertension as a primary or secondary diagnosis In three patients who were not bleeding frankly from esophageal varices the source of hemorrhage was gastric ulcer in two and undetermined in one Thus it appears that the prognosis is poorer in those in whom bleeding is due to or complicated by factors interfering with nutrition or the normal state of the gastrointestinal blood vessels

The ability to make a differential diagnosis on clinical grounds alone at time of active bleeding was limited Two aids in diagnosis of peptic ulcer were previous diagnosis of ulcer and presence of pain during bleeding Pain antecedent to bleeding proved unreliable Emergency x rays were done on patients with persistent or recurrent bleeding who could be operated on quickly if an ulcer diagnosis were made and on patients with recurrent bleeding of undetermined origin Study of films showed that a minimal degree of deformity of the duodenal bulb during emergency was not positive evidence of ulcer

In addition to conservative medical treatment free use was made of transfusions to prevent shock to replace lost

(7) New Engla d J Med. 241 473-478 Sept. 29 1949

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(8) G t oenter logy 12 597 616 Ap 1 1949

the mortality rate was not high enough to indicate surgery for the entire group However in patients over 50 mortality from exsanguination was 30 per cent The following criteria were *therefore tentatively proposed for surgical intervention in* peptic ulcer hemorrhage age 50 or over hematemesis in the hospital and proved peptic ulcer Of 40 patients in this group only 32 were operable Of these eight died during conservative treatment (25 per cent) In operable cases skilful surgery might be performed with only a 10 per cent mortality When specialized surgeons are available and surgery is not contraindicated patients of this group should be operated on following the first hematemesis in the hospital

[The significance of advanced age as the most important factor in death from hemorrhage is again emphasized by Pedersen Of interest too is the seriousness of hematemesis in contrast to melena the former implying rapid bleeding in his opinion—Ed]

Peptic Ulcer in Man Status of Ulcer Therapy is reviewed by S P Bralow H Kroll M Spellberg and H Necheles[9] (Michael Reese Hosp) Although it is generally accepted that peptic ulcer is a local weakness of the mucosa of the prepyloric segment or first portion of the duodenum precipitated and aggravated by acid pepsin secretion the evidence supporting this view is incomplete The ulceration may be a manifestation of a systemic neurocirculatory disorder Therefore treatment designed to neutralize acid content or inhibit pepsin activity must be considered merely symptomatic therapy which if properly used may or may not decrease the rate of recurrence

Sippy powders and other absorbable alkalis are unsatisfactory because of the incidence of alkalosis and of secondary acid secretion The favorable effects of milk protein cream and alkali are outweighed by the increased secretion of gastric juice frequent simulation of the reflex phase of gastric secretion repeated feedings and late stimulating effects of fat and alkali after absorption Among nonsystemic alkalis calcium carbonate magnesium carbonate and magnesium oxide or trisilicate are most useful but present disadvantages The calcium ion is constipating the magnesium ion produces laxation and carbonates are absorbed in sufficient amounts to produce alkalosis and acid rebound

Colloidal aluminum preparations which are at present

(9) Am J Dig st Dis 17 86 92 March 1950

widely used are clinically effective but produce constipation and relatively rapid elimination from the stomach These preparations may absorb phosphate and delay emptying time of the stomach The wide variation in carbonate content among the various brands may partly explain the difference in speed of action

The use of protein hydrolysate is directed at secondary nutritional deficiencies rather than at the cause of the ulcer Enterogastrone and sodium lauryl sulfate have not been proved superior to more conservative agents Hog s mucin would appear to be best physiologically since gastric mucus protects smoothes and lubricates the mucosa and acts as a natural antacid Its unpleasantness orally and the belief that its clinical effects are not impressive have led to a search for a synthetic gastric mucin which would comprise the theoretical ideal for an antacid Sodium carboxymethylcellulose has proved satisfactory because it is bland adheres to the gastroduodenal mucosa is unabsorbable not constipating and has a sufficient neutralizing ability

[This is a judicial appraisal of current treatment for ulcer especially from the standpoint of antacids Antacids leave much to be desired because they leave the stomach rapidly and their admixture with the gastric contents is often incomplete This is especially true of the less soluble antacids now in vogue The consequent resort to measures to prevent or reduce the amount of acid secreted to date has not been signally successful However progress is slowly being made in this direction and we look forward to the final report concerning sodium carboxymethylcellulose —Ed]

Continuous Drip Treatment of Peptic Ulcer, according to A M Clark[1] (Worcester England) requires minimal attention from the nursing staff can be used by the patient at home and is well tolerated Indications for the drip method are active ulcer recent hematemesis or melena and poor general condition

METHOD —The drip is given through a Ryle tube passed through the patient s mouth so that a point 14 in from the tip lies opposite the teeth The best solution is fresh milk citrated with 40 gr sodium citrate/pt delivered at a rate of 100 oz /24 hours Next most satisfactory is magnesium bicarbonate in 1 3 dilution with water of the B P solution delivered at a rate of 80 oz /24 hours Since the latter may have a laxative effect 15 minims of tincture of opium should be added to the drip reservoir twice daily In cases of anemia ferrous sulfate is given All patients should receive 50 mg ascorbic acid daily Those on the milk drip are given 1 gr phenobarbital twice

(1) Lancet 1 435 438 M 11 1950

daily The more seriously ill patients are confined strictly to bed on a milk drip without additional nourishment Others may have a routine gastric diet which excludes gross roughage chemical irritants and fried foods During the meal they may remove the tube The drip is continued for three weeks then after an additional week in bed the symptom free patient may be allowed up gradually If relapse is expected the patient is advised to set up a drip at home for use in the night or continuously over the weekend

Although in reacting with hydrochloric acid magnesium bicarbonate gives off carbon dioxide no case of alkalosis has been detected clinically or by chemical analysis

Of 29 patients with peptic ulcer demonstrable by x rays 19 had no evidence of ulcer 1 16 weeks after the drip ended Only one of this group was not symptom free

Modus Operandi of Carminatives Therapeutic Value of Garlic in Functional Gastrointestinal Disorders Carminatives defined as aromatic and pungent drugs used in flatulence and colic to expel gas and to diminish griping pains act by diminishing gastric movements and tension and by relaxing sphincters The uses and action of dehydrated garlic as a carminative were investigated by x ray and clinical studies *conducted by Frederic Damrau and Edgar A Ferguson*[2] (New York City)

In 25 patients with gastrointestinal complaints barium x rays were taken with and without administration of garlic to determine the effect of garlic on gastric and intestinal motility Six 4 75 gr tablets were given two with the barium meal two after two hours and two after four hours The gastric barium residue was larger with use of garlic indicating a sedative and delaying action on peristalsis

In 29 patients complaining of postprandial heaviness belching flatulence gas colic and nausea two garlic tablets were administered twice daily after lunch and dinner for two weeks Severity of symptoms was numerically rated to determine degree of benefit *after treatment Postprandial heaviness* regarded as consciousness of peristalsis was completely relieved in 15 patients partially relieved in 6 and not relieved *in* 4 Complete relief from belching occurred in 13 patients partial relief in 9 and no relief in 3 In 20 of 25 patients flatulence was relieved Complete or partial relief was obtained

(2) Rev Gastroent rol 16 411 419 May 1949

in 21 of 24 patients with colic and in 6 of 8 patients with nausea After two weeks of medication roentgenograms of these 29 patients showed delayed peristalsis

These results indicate that unidentified principles in garlic exert a sedative action on the Meissner plexus in the stomach and small intestines and probably on the Auerbach plexus causing a relaxation of tone and motility of the gastrointestinal tract The descriptive name gastroenteric allichalone (from *allium* garlic *chalone* to relax) was applied to these principles

Influence of Smoking on Management of Peptic Ulcer Patient Roger C Batterman and Irving Ehrenfeld[3] (New York Univ) considered two phases of this problem (1) the influence of tobacco smoking measured by the effectiveness of antacid therapy and incidence of acute exacerbations (2) the influence of smoking partially denicotinized tobacco on the peptic ulcer syndrome Of 108 patients studied 39 were non smokers and 26 discontinued smoking on first seeking treatment Excellent response to antacids was obtained in these groups with the incidence of exacerbations reduced to 11 5 and 17 5 per cent respectively Patients who continued to smoke regular tobacco showed only a 47 per cent effective response to antacid therapy with a 53 per cent incidence of exacerbations

Among the smokers 28 who had persistent symptoms and whose dietary and antacid response was poor were supplied with processed cigarettes (nicotine content averaging 0 85 per cent in contrast to 1 5 2 5 per cent in standard brands) Immediate improvement resulted in 78 6 per cent Eleven patients had complete relief from symptoms notably heartburn and epigastric pain Among those with moderate improvement symptoms persisted but were of undisturbing character Only 28 6 per cent of this group had acute exacerbations Reinstitution of camouflaged regular tobacco in 18 patients who had responded well to processed cigarettes caused a decreased response to antacids and a corresponding increase in exacerbations

The authors conclude from a comprehensive survey of the physiology and pharmacology of tobacco smoking that nicotine is probably an etiologic factor in gastrointestinal disor

(3) G t oe t logy 12 575 585 Ap 1 1949

ders and that tobacco smoking is detrimental to the peptic ulcer patient

Acid Neutralizing Power of Several Protein Hydrolysates and Other Substances Used in Ulcer Therapy Sidney M Samis and Franklin Hollander[4] (Mt Sinai Hosp New York City) compared the buffering action of four commercial protein hydrolysates and of unhydrolyzed protein alumina gel sodium bicarbonate whole fresh milk and other common antacids Buffer curves were determined by electrometric titrations with N/10 HCl under standardized conditions using a glass electrode The buffering power between initial pH and pH 3 5 was estimated by interpolation from the titration curves (pH 3 5 used as the boundary value between free and combined gastric acidities)

Three of the four protein hydrolysates showed a relatively high neutralizing power down to pH 3 5 sufficient to be effective antacids when given by mouth in daily dosage of 300 Gm (the minimum daily amount usually administered by Co Tui) Whereas 300 Gm of the most effective hydrolysate was capable of neutralizing 5 500 cc of N/10 HCl in vitro the same amount of acid required 45 Gm $NaHCO_3$ to bring the pH to 3 5 On a daily basis protein hydrolysates proved superior to alumina gel None of the other substances investigated could compare even to alumina gel in acid neutralizing action The authors concluded that the acid neutralizing function as well as the nutritive value of protein hydrolysates is highly important when these preparations are used in oral treatment of peptic ulcer

[One of the most encouraging reports it confirms Levy and Siler s observations (1942) regarding buffering action of a pancreatic hydrolysate of casein (amigen®) A pancreatic hydrolysate of lactalbumin (lactamin®) and Squibb s protein hydrolysate (pancreatic hydrolysate of casein) shared honors with amigen® in the study by Samis and Hollander —Ed]

Antipeptic and Antacid Therapy With Special Reference to Adsorbent Complexes of Calcium and Magnesium Phosphates *Etiology of persistent hyperchlorhydria* is obscure Only in a few cases can hyperchlorhydria be attributed to alcohol coffe or condiments Treatment must therefore be directed to neutralization of acid or to control of gland cell and nerve ending mechanisms

(4) Gastroent ol gy 12 665-670 Apr l 1949

Nathan Mutch[5] (Guy s Hosp London) reviews methods of diminishing gastric acidity and discusses the antipeptic action of antacids with particular reference to calcium and magnesium phosphate compounds The most important min eral antacids are magnesium oxide carbonate phosphate tri silicate and basic trisilicate calcium carbonate phosphate and silicate aluminum hydroxide basic carbonate phosphate aminoacetate and aluminum sodium silicate Except for mag nesium oxide basic magnesium trisilicate and sodium bicar bonate alkalinizing agents to be used with caution these re duce HCl concentration to various extents within desirable clinical range In all there is wide discrepancy between esti mated acid secretion and amount of antacid necessary for neu tral interaction

The digestive action of pepsin is thought to have an erro sive effect on the peptic ulcer base This effect can be pre vented by several means (1) Overneutralization to pH 5 or more abolishes pepsin activity However it is not usually feasible to reduce acidity continuously to this level with ant acids (2) Pepsin can be destroyed by aluminum salts (3) Ad sorption of pepsin on kaolin and silica gel reduces its activity but does not destroy its digestive function (4) Magnesium trisilicate and basic and activated calcium and magnesium phosphates also adsorb pepsin forming nonproteolytic com plexes

Activated phosphates are complexes of hydrated silica and tribasic calcium or magnesium phosphate they are insoluble in water but react with HCl to form soluble chlorides free phosphoric acid and hydrated silica residue These silica com plexes have greater adsorptive action than any dried free silica gel available In 10 patients with chronic peptic ulcer and 13 new patients activated phosphates were given as the sole antacid in doses of 2 drachms every two hours with ex cellent clinical results They also proved adequate in test meal fractional studies

Effect of Urecholine* on Stomach Intestine and Urinary Bladder was investigated by I F Stein Jr and Karl A Meyer[6] (Cook County Hosp) A balloon was placed in the vagotomized stomach of each of 12 patients and kymographic

(5) La t 1 859 863 M y 1 1949
(6) J A M A 140 5 525 J 11 1949

tracings were made after administration of urecholine® In each of three patients 5 mg urecholine® given subcutaneously increased gastric motility in 5 10 minutes (Fig 115) In eight patients 10 mg given orally produced moderate to pronounced increase in gastric motility in 30 minutes to 1½ hours lasting 30 minutes to 3 hours Sublingual administration of 10 mg caused only slightly increased gastric motility in one patient whereas 25 mg produced adequate stimulation Clinical observations on 10 additional patients with symptoms of gastric retention after vagotomy showed that 20 30 mg of

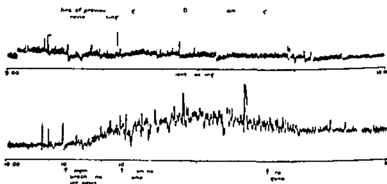


Fig 115—Effect of cb l ® on g t c m t l ty (C rtesy of St I F Jr a d Meye K A J A M A 140 522 525 J e 11 1949)

the drug three times daily before meals gave satisfactory results in all Urecholine® 10 20 mg given orally for 10 20 days after gastric resection without vagotomy relieved four of five patients with symptoms of poor gastric emptying or retention The patient who was not relieved was found at reoperation to have a kink which obstructed the gastrojejunal anastomosis

Of 20 patients with adynamic ileus 13 passed gas and feces 10 minutes to 2 hours after administration of urecholine® Those with severe ileus received 5 mg subcutaneously followed three hours later by 25 30 mg orally or sublingually The dosage was repeated four times a day if necessary Oral administration of 20 30 mg urecholine® usually relieved mild postoperative abdominal distention In five patients gradual improvement occurred in two to three days in two a single dose of urecholine® failed to relieve distention

Of 18 patients with postoperative urinary retention 15 voided 3 10 minutes after subcutaneous injection of 5 mg urecholine* The drug gave relief from urinary retention in one of two patients with transverse myelitis and in one with cord bladder In a second patient with cord bladder evacuation of the bladder was completely controlled by urecholine* In four patients with urinary retention urecholine* promptly increased intravesical pressure to a maximum in 3 10 minutes The catheter through which manometric readings were taken was removed 10 minutes after the drug was given Each patient voided spontaneously in one minute

Theoretical contraindications to use of urecholine* include unhealed gastrointestinal anastomosis peritonitis mechanical intestinal obstruction pregnancy and asthma

Results show that urecholine* is a potent parasympathomimetic drug of low toxicity which stimulates gastric motility in the normally innervated and in the vagotomized stomach It is of definite value in treatment of both adynamic ileus and postoperative urinary retention although its effective use in cord bladder must still be determined

[This is an encou aging report but one does occasionally meet with di appointing r sults with th drug in the treatment of postoperative mor b d physiologic conditions —Ed]

Dry Feedings in Gastric Motor Delay Jerome E Cook and Edward C Malewitz[7] (Jewish Hosp St Louis) evaluated use of dry diets with all fluids administered parenterally for treatment of gastric or duodenal ulcers associated with gastric motor delay Only patients who had failed to improve on conventional Sippy or Meulengracht diets were included The diet consisted mainly of finely divided hard boiled eggs dry cottage cheese cooked cereal without added cream crackers minced chicken mashed potatoes and rice Butter was added to the cereal foods The usual antispasmodics antacids and sedatives were continued Initially nightly aspirations of gastric residuals were done

Gratifying results were obtained in several cases one of which is included here

Man 67 had hunger pains for five years and had lost 80 lb despite the usual Sippy regimen Constant vomiting had been present for six weeks X rays showed over 50 per cent gastric retention in five hours and evidence suggestive of duodenal ulcer On a Sippy

(7) Am J D g t D 16 2 4 J 1949

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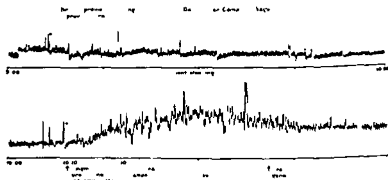


Fig 115—Effect of urecholine® on gastric motility (Courtesy of St I F Jr and Meyer K A J A M A 140 52 5 5 June 11 1949)

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that among 31 per cent of patients reporting a favorable course only 15 3 per cent remained entirely free from ulcer distress In 19 per cent slight but frequent recurrence of trouble was reported Of the 40 per cent who had a serious course 3 9 per cent died of peptic ulcer and the remainder had definite relapses leading to further treatment or operation Of the deaths attributed to ulcer 74 per cent occurred during the year following treatment and 2/3 were associated with opera tions Mortality was greatest among older patients The prog nosis seemed somewhat more favorable for gastric ulcer pa tients than for those with duodenal ulcers 21 9 per cent of the former remaining totally free from distress compared with 12 7 per cent of the latter Duodenal ulcer however was asso ciated with a lower mortality rate Duodenal ulcer patients with a history of more than five years showed a pronounced tendency to relapse (87 5 per cent) particularly those who had undergone previous treatment Gastric ulcers showed a greater tendency to hemorrhage with the risk greatest when hemorrhage had previously occurred The mortality for hem orrhage in the entire group was 1 6 per cent for perforation 1 2 per cent

During the observation period 135 patients were operated on 68 9 per cent with favorable results Because in gastric surgery there is now a low primary operative mortality the authors believe most peptic ulcers can be treated surgically particularly those refractory to relapse prophylaxis

***Peptic Ulcer Cases Reviewed after 10 Years Effect of* Medical Treatment and Indications for Gastrectomy** Lau rence Martin and Ninian Lewis[9] (Addenbrooke s Hosp Cam bridge) believe that the only way of assessing value of treat ment of chronic disease such as peptic ulcer is by a long term follow up survey which shows how the natural course has been influenced They interviewed and examined 195 patients (Table 1) *most of whom were treated medically* A few were in need of operation because of perforation Cases of anas tomotic ulcer were included under primary ulcer Deaths as a direct result of ulcer are listed in Table 2 and deaths from other causes are listed in Table 3

There were 123 gastric and 62 duodenal cases Fifty per cent of the gastric and 39 per cent of the duodenal ulcers were

(9) La t 2 1115 1120 D 17 1949

diet with antispasmodics antacids and sedation vomiting continued and nocturnal gastric residuals of 450 cc were aspirated Immediate relief followed use of dry feedings and intravenous fluids Diminution in nightly residuals occurred and the patient showed a weight gain after five days Gastric retention decreased to 25 per cent in five hours and fluids by mouth were then permitted

The mechanical factor of peristaltic inhibition by fluids but not by solids and the psychologic value of change from liquid to solid food as well as the added caloric value of concentrated food were considered of importance in the success of therapy The smaller volume of feedings may help a dilated stomach regain tonus Complete withdrawal of oral feeding may not be necessary or advantageous in pyloric obstruction dry feedings although not a treatment of choice in peptic ulcer or other lesions may satisfactorily tide a patient over a period of gross gastric retention

[Empirically perhaps but for years my surgical colleagues have resorted to a dry diet under the circumstances mentioned usually with salutary effect The necessary fluids were administered orally 2 4 hours after feedings or parenterally when circumstances required it —Ed]

Postinvestigation of 687 Medically Treated Cases of Peptic Ulcer has led Haqvin Malmros and Tor Hiertonn[8] (Orebro Central Hosp Sweden) to conclude that ulcer disease has a poor prognosis Only cases in which diagnosis had been verified by x ray and which had been observed for 7 10 years after treatment were included Of the 687 patients 495 had duodenal and 192 gastric ulcers On admission for treatment 18 per cent had severe manifest hemorrhage associated with gastric ulcer in 50 patients with duodenal in 75 In 5 2 per cent previous operation for perforation had been done

Ulcer treatment included bed rest in the hospital for three to four weeks and the following diet liquid or semi liquid diet the first week pureed the second and pureed plus easily digested solids the third Abundant calories were supplied throughout treatment even in hemorrhagic cases A mixture of magnesium subcarbonate bismuth subsalicylate and extract of belladonna was given three to five times daily Most patients also received phenobarbital 0 025 Gm three to four times daily

Preliminary result of treatment was good 93 5 per cent of patients showing no crater on x ray Postinvestigation results however based on the history and hospital records showed

(8) A t m d S d n v 133 9 25 1949

that among 31 per cent of patients reporting a favorable course only 15.3 per cent remained entirely free from ulcer distress In 19 per cent slight but frequent recurrence of trouble was reported. Of the 50 per cent who had a serious course 3.9 per cent died of peptic ulcer and the remainder had definite relapses leading to further treatment or operation. Of the deaths attributed to ulcer 74 per cent occurred during the year following treatment and 2.3 were associated with operations Mortality was greatest among older patients The prognosis seemed somewhat more favorable for gastric ulcer patients than for those with duodenal ulcers 21.9 per cent of the former remaining totally free from distress compared with 12.7 per cent of the latter Duodenal ulcer however was associated with a lower mortality rate. Duodenal ulcer patients with a history of more than five years showed a pronounced tendency to relapse (87.5 per cent) particularly those who had undergone previous treatment. Gastric ulcers showed a greater tendency to hemorrhage, with the risk greatest when hemorrhage had previously occurred. The mortality for hemorrhage in the entire group was 1.6 per cent, for perforation 1.2 per cent.

During the observation period 13[illegible] patients were operated on 68.9 per cent with favorable results. Because in gastric surgery there is now a low primary operative mortality the authors believe most peptic ulcers can be treated surgically particularly those refractory to relapse prophylaxis

Peptic Ulcer Cases Reviewed after 10 Years Effect of Medical Treatment and Indications for Gastrectomy Lawrence Martin and Vivian Lewis[3] (Addenbrooke's Hosp., Cambridge) believe that the only way of assessing value of treatment of chronic disease such as peptic ulcer is by a long term follow up survey which shows how the natural course has been influenced. They interviewed and examined 195 patients (Table 1) most of whom were treated medically A few were in need of operation because of perforation. Cases of anastomotic ulcer were included under primary ulcer Deaths as a direct result of ulcer are listed in Table 2 and deaths from other causes are listed in Table 3

There were 123 gastric and 62 duodenal cases Fifty per cent of the gastric and 39 per cent of the duodenal ulcers were

(3) Lancet 2:1117, Dec. 1[illegible], 1949

diet with antispasmodics antacids and sedation vomiting continued and nocturnal gastric residuals of 450 cc were aspirated Immediate relief followed use of dry feedings and intravenous fluids Diminution in nightly residuals occurred and the patient showed a weight gain after five days Gastric retention decreased to 25 per cent in five hours and fluids by mouth were then permitted

The mechanical factor of peristaltic inhibition by fluids but not by solids and the psychologic value of change from liquid to solid food as well as the added caloric value of concentrated food were considered of importance in the success of therapy The smaller volume of feedings may help a dilated stomach regain tonus Complete withdrawal of oral feeding may not be necessary or advantageous in pyloric obstruction dry feedings although not a treatment of choice in peptic ulcer or other lesions may satisfactorily tide a patient over a period of gross gastric retention

[Empirically perhaps but for years my surgical colleagues have resorted to a dry diet under the circumstances mentioned usually with salutary effect The necessary fluids were administered orally 2-4 hours after feedings or parenterally when circumstances required it —Ed]

Postinvestigation of 687 Medically Treated Cases of Peptic Ulcer has led Haqvin Malmros and Tor Hiertonn[8] (Orebro Central Hosp Sweden) to conclude that ulcer disease has a poor prognosis Only cases in which diagnosis had been verified by x ray and which had been observed for 7 10 years after treatment were included Of the 687 patients 495 had duodenal and 192 gastric ulcers On admission for treatment 18 per cent had severe manifest hemorrhage associated with gastric ulcer in 50 patients with duodenal in 75 In 5 2 per cent previous operation for perforation had been done

Ulcer treatment included bed rest in the hospital for three to four weeks and the following diet liquid or semi liquid diet the first week pureed the second and pureed plus easily digested solids the third Abundant calories were supplied throughout treatment even in hemorrhagic cases A mixture of magnesium subcarbonate bismuth subsalicylate and extract of belladonna was given three to five times daily Most patients also received phenobarbital 0 025 Gm three to four times daily

Preliminary result of treatment was good 93 5 per cent of patients showing no crater on x ray Postinvestigation results however based on the history and hospital records showed

(8) Acta m d S d av 133 29 25 1949

chance of hemorrhage was about 1 3 for all gastric and duo denal ulcers and the chance of dying of it was 1 25 About 80 85 per cent of the patients with bleeding were aged 40 70 About 60 per cent of patients with 10 years or more of activ ity had hemorrhage Mortality from this complication was highest in patients over 50 There was a 1 3 chance of per foration for all cases either within 5 years of onset or after 10 years with only a small incidence in the intervening period About 80 per cent of gastric perforations occurred between ages 40 and 70 compared with 60 5 per cent of duodenal per forations

Gastrectomy should not be recommended if a reasonable chance exists that an ulcer will heal Medical treatment of gastric ulcer is justified by the fact that about 30 per cent in this series healed without surgery It should be remembered that the mortality from gastroduodenal hemorrhage is influ enced greatly by the age of the patient and scarcely at all by the length of ulcer history Each case must be judged on in dividual circumstances but in general gastrectomy is advo cated for peptic ulcer after 10 years duration or whenever possible by age 50 If this were carried out invalidism com plications and deaths from chronic peptic ulcer would be greatly diminished

[Reports of similar nature from sources at home and abroad are dis appo nting and leave little room for complacency or self satisfaction on the part of physician and special st —Ed]

Immediate Results of Partial Gastrectomy for Peptic Ulcer In 101 cases analyzed by B B Milstein[1] (Univ Col lege Hosp London) partial gastrectomies were performed for peptic ulcer without pyloric stenosis in 72 cases for non malignant organic pyloric stenosis in 28 and for hypertrophic pyloric stenosis in 1 Indications for surgery included in tractability recurrence repeated hematemeses pyloric ob struction hemorrhage suspected cancer and hour glass con tracture Many patients had undergone lengthy medical treat ment No patients were refused operation because of age or the presence of complications Except in acute hemorrhage all complications related to the ulcer were treated before surgery Suspected activity of the ulcer was treated by at least three weeks bed rest and a suitable gastric diet

The following lesions were present at operation 38 gas

(1) La et 1 514 517 M 6 1949

inactive following various treatments A history of character istic ulcer dyspepsia during the preceding five years was con sidered activity Of the 96 gastric and 43 duodenal cases treated medically 44 per cent of the former and 32 5 per cent of the latter were inactive In most of the remainder perse verance with a regular or occasional regimen of diet and alkali had little effect on the healing of the ulcers or the incidence

TABLE 1

Ty e of Ulce	De	Traced	U	Tota
Gastric	97	123	11	231
Duodenal	35	62	8	105
Gastric + duodenal	10	10		20
Total	142	195	19	356

TABLE 2—Deaths as Direct Result of Ulcer

Cau	G c	Dlodeн l	Gastric + Du enal	T t
Hemorrhage	9	5	1	15
Perforation + operation	21	7	2	30
Perforation no operation	5	2		7
After gastrectomy	6	1	2	9
After gastroenterostomy	3	3		6
After other operations for ulcer	5	2	1	8
Total	49	20	6	75

TABLE 3—Deaths from Other Causes

Typ o Ulcer	U Ac i	Ul er In c e	Act ty Unknown	T
Gastric	16	9	17	42
Duodenal	6	1	8	15
Gastric + duodenal	1		3	4
Total	23	10	28	61

of complications and consequently did not influence the natu ral course of the disease For gastric ulcer patients there was a significantly greater chance of healing and inactivity 10 years later if there was a short rather than a long history at time of hospitalization In both groups successful medical treatment was unlikely in more than 50 per cent of those ad mitted to the hospital

The generally accepted indications for gastrectomy are in tractable chronicity hemorrhage perforation and malignant change Gastrectomy should be considered in all patients with peptic ulcers of 10 years duration for beyond this point the chances of rapid healing diminish In this series the

and the avoidance of secondary operations for obstruction were attributed to preoperative rest strict suture technic and routine postoperative gastric suction The author recognizes that the strict suture technics by prolonging the operation increase the risk of contamination

Postoperative complications occurred in 51 per cent of all operations although the incidence dropped 39 per cent in the later cases Chemotherapy early ambulation pre and post operative exercises were possible contributing factors Wound infection chiefly staphylococcic was the outstanding single complication Local application of penicillin to wound layers *during closure and use of stainless steel sutures are recom* mended for prevention of such persistent infections

Symptomatology and Diagnosis of Gastric Cancer John S LaDue Paul J Murison Gordon McNeer and George T Pack (Memorial Hosp New York City) studied the records of 1 117 patients with gastric cancer to determine whether any correlation existed between duration and signs and symp toms and resectability rate The incidence of resectability in patients with gastric cancer was 39 8 per cent and the rate of five year survival varied from 42 8 per cent for patients with out nodal metastases to 24 2 per cent for those in whom disease *was not confined to the stomach When cancer involved the* cardia resectability rate was 59 per cent

The frequency and multiplicity of symptoms in patients with inoperable and operable gastric cancer was essentially the same except that dysphagia was twice as common with inoperable carcinoma In order of frequency symptoms were loss of weight (83 5 per cent) pain vomiting bowel dis turbances anorexia dysphagia nausea weakness eructa tion hematemesis and rapid satiation (4 6 per cent) Weight loss over 41 lb was usually associated with inoperable gastric cancer The more rapid the weight loss the more striking are hepatic dysfunction *hypoproteinemia inanition and other* metabolic deficiencies Pain was the initial symptom in 41 per cent dysphagia in 11 9 per cent and anorexia in 8 0 per cent When the cardia was involved dysphagia was the first symp tom in 40 per cent Pain was more common when cancer in volved the lesser curvature of the body of the stomach and frequently simulated angina pectoris Anorexia was more fre

(2) A h S g 60 305 33 F bru y 1950

tric ulcers 45 duodenal 6 gastric and duodenal 7 pyloric 5 anastomotic and 1 hypertrophic pyloric stenosis Pyloric stenosis was present in 28 cases In all cases partial gastrectomy with anastomosis of the gastric remnant to the jejunum was performed Three principles were consistently observed (1) In mobilizing the stomach mass ligature of tissues was

POSTOPERATIVE COMPLICATIONS (102 OPERATIONS*)

Com ication	To	Befo e Jan 1945	A e J n 1945
Superficial wound infection	15	9	6
Deep wound infection	2	1	1
Atelectasis	11	9	2
Pyrexia of unknown origin cough bronchitis	5	3	2
Burst abdomen	5	4	1†
Bronchopneumonia	2‡	0	2‡
Subhepatic abscess	2	0	2
Lung abscess	2	2	0
Pulmonary embolus	2	2	0
Peritonitis	1‡	0	1‡
Persistent hiccup	1	0	1
Femoral thrombosis	1	1	0
Postoperative gastric bleeding	1§	1	0§
Postoperative melena	1	0	1
Dysentery bloody diarrhea	2	1	1
Penicillin rash	1	0	1
Hydropneumothorax	1‖	0	1‖
Tension pneumothorax and congestive cardiac failure	1‖	0	1‖
Pressure palsy of arm	1	0	1
Empyema	1	1	0
Total complications	58	34	24
Total cases with complications	52 (51%)	34 (61%)	18 (39%)

* F fty s x bef 1945 46 fte
† Sk n o ly
‡ O e d th h
§ Ope t on fo hem h g (l o nclud d bhepat c ab)
‖ F llowed nte tal blo k

avoided vessels being ligated separately or in small groups (2) Clamps were not used except on edges of gut that were subsequently invaginated (3) Closures and anastomoses were made in two layers with a continuous all coats catgut suture and interrupted seromuscular sutures of fine serum proof silk A Ryle tube placed in position before operation permitted intermittent gastric suction until the fluid balance became positive

The low mortality rate of 2 per cent despite the many poor risk cases the absence of significant gastric retention

x ray in 91 5 per cent of 1 022 patients In 305 patients the inci dence of positive diagnosis of 86 9 per cent by x ray study was raised to 96 4 per cent when gastroscopy was used

[The results of this instructive clinical study dovetail with those of large experience in this field in which there is vast room for improve ment —Ed]

Fever Common Symptom in Carcinoma of Stomach Doris A Berlin and William B Porter[3] (Med College of Vir ginia Hosp) studied the histories of 69 patients during 81 admissions Any oral temperature of 99 F or above was con sidered fever No fever was recorded in 14 81 per cent In 24 69 per cent fever was ascribable to infection or causes other than neoplasm Fever was classed as of doubtful origin in 12 35 per cent Neoplasm appeared to be the only cause of fever in 49 15 per cent

In the group with fever due to neoplasm temperature ele vation was intermittent rather than continuous Rises occurred irregularly and were not sustained During any 24 hour period a typical patient would have several normal readings and per haps one or two above normal In some cases fever appeared only once or twice during a week There was no predilection for either a nocturnal or a diurnal appearance

Of 11 patients with fever whose stomachs were removed surgically only 3 were reported as having intact mucosa Of 12 patients without fever 2 had ulceration Apparently fever may occur in the absence of ulceration or ulceration may oc cur in the absence of fever The series did not include suf ficient cases of nonmetastatic carcinoma to permit statistical evaluation of the significance of metastatic lesions in produc tion of fever

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THE LIVER PANCREAS AND GALLBLADDER

Observations on Biliary Pancreatic Dynamics in Normal Human Previous studies have usually been conducted on cholycystectomized patients with a T tube in the common duct John D Ryan Henry Doubilet and John H Mulholland[4] (New York Univ) carried out similar studies on an other wise healthy young man with an external fistula of the right

(3) V g M Monthly 77 59 65 F bru ry 1950
(4) G t oent logy 13 1 8 J ly 1949

quent with pyloric and prepyloric cancer The greater curvature of the fundus is the silent region of the stomach and when the cancer site it is seldom responsible for pain or interference with passage of food

Stomach cancer may become inoperable before the patient has any symptoms but may be operable when symptoms presumably due to cancer have been present for two years When symptoms have been present 18 36 months operative mortality is three times as great as when complaints are of shorter duration

There were 155 patients who had gastrointestinal symptoms for more than two years Of these 53 had a history of ulcer like symptoms and 102 gave a vague story of indigestion In many of these patients a change in symptoms developed which could have been an important clinical clue to the development of stomach carcinoma

There was a palpable epigastric mass in 57 per cent of patients with inoperable gastric cancer and in 42 per cent of those in whom it was operable This does not necessarily indicate inoperability Aspiration liver biopsy or peritoneoscopy should be used if peritoneal carcinosis or hepatic metastasis is suspected With these aids about 50 per cent of patients with these lesions may be spared the discomforts hazards uselessness and expense of exploratory laparotomy Analysis of physical findings disclosed that 11 per cent of the patients examined had one or more signs such as signal nodes Blumer s shelf ascites jaundice obviously nodular liver or other pelvic implants indicating the inoperable nature of the cancer

Achlorhydria was found in 65 0 per cent of patients with inoperable gastric cancer and in 51 1 per cent of those in whom carcinomas were resectable The incidence of achlorhydria was greater in those with extensive carcinoma or high grade lesions Excessive amounts of free hydrochloric acid were twice as frequent in patients with benign gastric ulcer as in those with gastric cancer and three times as often as in normal adults aged 60 65 No acidity occurred in the same proportion in normal persons of cancer age in patients with gastric cancer and in those with benign gastric ulcer A relatively high degree of achlorhydria was found in those with polypoid or infiltrating gastric cancers

An unequivocal diagnosis of gastric cancer was made by

hepatic duct the result of a bullet wound Their results paral leled observations on patients with diseased biliary tracts

Morphine sulfate 10 mg was administered subcuta neously followed 15 minutes later by 35 per cent diodrast® solution injected slowly through the fistula by a Foley cathe ter X rays were taken during this and subsequent injections at 10 minute intervals At the first injection dye outlined the intra and extrahepatic ducts and partially filled the gall



F g 1 0 (l ft) —F lm m d ft p m f ph ct f Odd w p od ed by HCl j ct on to d oden m D od t j t d b ough h t l outl d wh l b l ry t ct d p od ed fl x p p d ct (w)

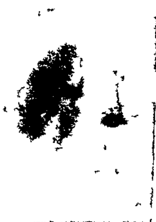
F g 1 1 (ght) —F lm m d fi m te ft j ct f morph b w g comp f t m l po t f mm d ct (w) d bse f p eat d ct al zat \ t w g f mp lt f g llbl dde d p t sed p

(C rt y f Ry J D et l G oent l g 13 1 8 J ly 1949

bladder (Fig 116) Thirty minutes after administration of morphine the gallbladder filled completely and the terminal end of the pancreatic duct was visualized (Fig 117) Little dye entered the duodenum Epigastric pain and nausea occurred with each injection of diodrast® and consequent distention of the bile ducts Immediate inhalation of amyl nitrite produced relaxation of the sphincter rendered spastic by morphine al lowing the dye to pass rapidly into the intestine (Fig 118) The common duct emptied completely and could not be vis ualized five minutes later (Fig 119) The gallbladder relaxed









F g 116 (top left) —F lm m d 15 m ut afte dm n trat on of morph ne show g b lary t a t o tl ed w th d d ast® a d g llbl dd b g g t fill No d odrast® has p s d t d od m

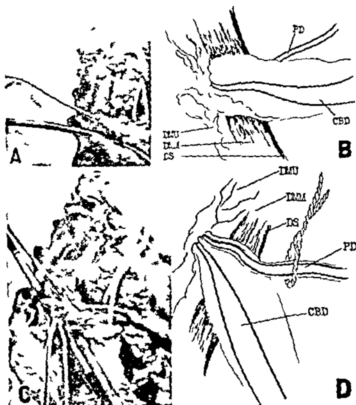
F g 117 (t p ght) —W th co t d j t g llbladd gra l lly filled d fo ced ome d od t® nto du d m A ow d c te p t c d t t b llet ly g n b dy of ele th th c v t b (F cl ty t m l e d of d t th s figu e d Figu e 116 we o tl n d)

F g 118 (bottom left) —Dy n d te d d b l y t ct p sed p dly to d de um after sph ncte r of Odd w r l xed by amyl n t te h l t

Fig 119 (bottom ght) —F lm m de fi m t aft myl t it h l t B le d cts no l ge v al ed

(Co rtesy of Rya J D f J Gast oent logy 13 1 8 J ly 1949)

physiologic In one third of the specimens the duct was extra pancreatic in one third intrapancreatic and in one third par tially intrapancreatic *An elevated caruncle depressed in* 24



F g 1 ~I m f tr d od l c mmon b l d ct w norm l w th ck n of wall Ext ad od n l mm b le d ct wa extrahep t c f 50 per t of ta pa cr t c co P n e tic d ct w n rmal u P pill wa 15 9 mm. long d 6 4 mm w d d od al w ll w 12 7 mm. w de. *A* d *B* p be pa c t d ct u et l cath t n ommon b l duct. *C* and *D* wall f d ct e ted (f t y f Ste l g J A Re G st oe t) 16 8 1845 Novem be 1949)

per cent of specimens and level with adjacent duodenal mu co a in 22 per cent marked the termination of the duct A typical dissection is shown in Figure 122

A papilla representing enlargement of the wall of the

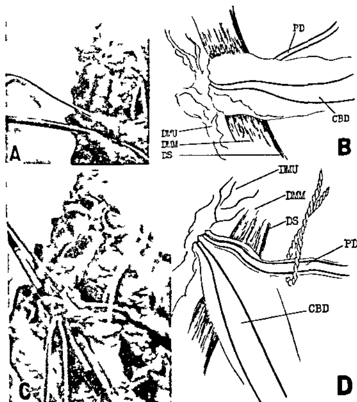
and did not empty While 10 cc of N/10 HCl was rapidly injected into the duodenum through a Rehfuss tube diodrast* was instilled through the biliary fistula Figure 120 shows that the resulting spasm of the sphincter of Oddi forced dye into the pancreatic duct demonstrating the common biliary pancreatic passageway An x ray taken five minutes after subcutaneous injection of morphine sulfate 10 mg showed muscular spasm of the duodenal wall (Fig 121) The lower end of the common duct was compressed and tonus of the gallbladder increased

To demonstrate the effect of a fat meal on intraductal pressure normal saline was perfused into the biliary tract through the fistula and syphoned from the duodenum through a Rehfuss tube A kymographic tracing showed intraductal pressure of 150 mm Two minutes after administration of a 20 cc mixture of olive oil cream and bacon drippings intraductal pressure rose 20 mm Tonic contractions of the gallbladder were noted and a flow of dark concentrated bile appeared in the Rehfuss tube Injection of 10 cc N/10 HCl into the duodenum produced spasm of the sphincter of Oddi Intraductal pressure rose to 190 mm water and then fell rapidly as the effect of the acid decreased Tonus rhythm reappeared when intraductal pressure reached 170 mm At the termination of the experiment intraductal pressure fell gradually to 120 mm These results were comparable with those obtained previously only in animals

Termination of Common Bile Duct Julian A Sterling[5] (Univ of Pennsylvania) studied 80 dissections of the termination of the common bile duct of which 50 were detailed and included microscopy The common bile duct traveled a double S shaped course The proximal curve was extraduodenal and the lumen of the duct in this area averaged 6 3 mm in diameter The distal curve within the duodenal wall was short In the last few centimeters the lumen of the duct tapered like a cone or funnel terminating as a filamentous canal The diameter of the orifice in the duodenal canal averaged 2 mm It would therefore be impossible for a calculus larger than 3 mm in diameter to pass normally through the termination of the duct into the duodenum Likewise passage of large Bakes dilators in surgical manipulation is considered un

(5) Rev Ga troente ol 16 8 1 845 No mber 1949

physiologic In one third of the specimens the duct was extra pancreatic in one third intrapancreatic and in one third partially intrapancreatic An elevated caruncle depressed in 24



F g 12 —L m f t d od l comm n b l d ct w m l w th k w ll Ext d od nal mm b l d ct w t h p t f 50 p t f ts p t c P t d t w mal P p ll w 15 9 mm. long d 6 4 mm w d d d l w ll w l 7 mm. w d *A* d *B* pr be p t c d ct t l th t l n common b le d ct. *C* d *D* w ll f d t erted (Cou te y f Ste l g J A R G t oe t l 16 8 1 845 Novem be 1949)

per cent of specimens and level with adjacent duodenal mucosa in 22 per cent marked the termination of the duct A typical dissection is shown in Figure 122

A papilla representing enlargement of the wall of the

termination of the duct was found due to an increase in the width of the walls caused by presence of a sphincter muscle An ampulla or dilatation of the duct was not observed The papilla averaged 14 1 mm in length and 3 4 mm in thickness In 45 of 46 specimens the mucosa within the papilla formed many folds and reduplications Often these valvules were not fused but were freely movable within the lumen of the common duct so that mucosal fringes extended within the duodenal canal or into a common channel On microscopy muscular and fibrous tissues were found in the valvule In 32 of 50 specimens separate openings for pancreatic and common bile ducts were observed In 18 specimens (36 per cent) presenting a common channel average length of the papilla was 14 4 mm that of the common channel 4 4 mm The common channel was equal in length to the papilla in one specimen In only 1 of 50 specimens did the common channel form outside the duodenal wall Three sets of sphincters were identified in the medial third of the papilla The proximal two surrounded each duct separately the distal one both ducts

The low reported incidence of reflux into the pancreatic duct (just under 16 per cent) as shown on cholangiograms is substantiated by the few specimens found with a long common channel Since the length of the papilla was 1 cm greater than that of the common channel the muscle proximal to the channel (sphincter of Oddi) would prevent interductal reflux Sterling recommends that the term ampulla be deleted from use with reference to any portion of the termination of the common bile duct The expanded distal portion of the duct should be called the papilla Its termination within the duodenum could be called the caruncle or the papilla of Vater

Extrahepatic Biliary System Its Phylogenesis is described by J H Louw[6] (Univ of Cape Town) who has personally dissected the biliary systems of 38 species representing all the vertebrate classes and every placental order

A close relation was found between the phylogenetic development of an animal and the anatomy of its biliary system The primitive biliary system is a complex structure consisting of multiple hepatic ducts and a large gallbladder The biliary systems of more highly specialized species have a simpler structure Accessory hepatic ducts disappear and the

(6) Cl n Proc C pe Town Po t G d M A 8 185 220 r

gallbladder tends to be small Biliary systems of species whose body forms have departed considerably from that of their ancestors are extremely simple No gallbladder is present and there is no compensatory dilatation of the bile ducts

There is a similar relation between the pattern of the gastrointestinal tract and that of the biliary system and both are related to the dietary habits of the animals Species with simple digestive canals have a primitive form of biliary apparatus They are carnivorous and insectivorous Species with minor complexities of the gastrointestinal tract usually possess a gallbladder but no accessory hepatic ducts They are insectivorous and herbivorous Species with the most highly specialized alimentary systems tend to lose the gallbladder They are essentially herbivorous In general the gastrointestinal tract adapts itself more readily to changes in the body form and mode of life of the animal Anatomic complexities of the digestive system precede structural changes in the biliary tract A gallbladder is present even in herbivorous marsupials which possess most complex gastrointestinal tracts but on the other hand no species with a very simple alimentary tract lacks a gallbladder

Functional activity of the biliary system is progressively diminished from the lower to the higher vertebrates This together with progressive loss of form is an indication of the declining needs for a highly efficient bile concentrating mechanism Since bile is necessary for digestion and absorption of fats it is significant that carnivora possess the primitive type of biliary system while herbivora tend to lose the complex biliary system The human biliary system occupies an intermediate position in the phylogenetic development of the biliary system Accessory hepatic ducts represent the arrangement of the primitive biliary system Congenital absence of the gallbladder represents the pattern of biliary system of species which have become highly specialized Anomalies encountered represent different stages in the phylogenetic development of the biliary system

Comparison of Pain Produced Experimentally in Lower Esophagus Common Bile Duct and Upper Small Intestine with Pain Experienced by Patients with Diseases of Biliary Tract and Pancreas Pain localization alone is insufficient to identify clinically the visceral structure involved William P

Chapman Rudolfo Herrera and Chester M Jones[7] (Harvard Univ) compared experimentally produced and clinical pain to determine whether pain arising from bile ducts and duodenum may have an identical area of localized reference in any given patient Of nine patients studied seven had biliary tract disease and two pancreatitis Experimentally pain was produced by distending the common duct cardiac end of the esophagus and duodenum or upper jejunum The person was asked (1) to report any sensation (2) to outline the area

TABLE 1—COMPARISON OF PAIN EXPERIMENTALLY PRODUCED IN UPPER ABDOMINAL VISCERA

\ scer S mu a d	To al Cases	Cas s w th I f tical P in	Cas s w th Diff e t P
Esophagus upper small intestine and common duct	9	3	6
Esophagus and upper small intestine	9	3	6
Esophagus and common duct	9	5	4
Upper small intestine and common duct	9	7	2†
Duodenum and jejunum	5	5	0

I d t gu h bl to qu l ty l at n nt n ty d d t
†Pa w tl e s m e c pt fo d ffe e n rad t

TABLE 2—PAIN EXPERIMENTALLY PRODUCED REPRODUCING CLINICAL PAIN OF BILIARY TRACT AND PANCREATIC ORIGIN

Visce a Stimulated	Tot l Cases	Cases w th I ti Pa	C s w D f n P n
Common duct	9	7	2†
Upper small intestine	9	7	2†
Esophagus	9	4	5

S m q l ty loc t d d t
†Pa n w the m cept f d ff n d t

of sensation (3) to describe quality intensity depth and radiation of sensation and (4) to compare the sensation with his clinical pain In each viscus studied the test was repeated at least three times

In the same patient similarities were found among pains induced by distention of different viscera in terms of location radiation quality and intensity However the amount of distention necessary to elicit pain of comparable intensity varied among patients Pain from distention of the common duct and upper small intestine was the same in seven patients and different in two When the lower esophagus was included in the comparison distention produced identical pain in only three patients Results are summarized in Table 1 Results of com

(7) S g Gy ec & Ob t 89 573 58 N mb 1949

parison of clinical pain with that induced experimentally are given in Table 2 In seven patients clinical pain was reproduced by distention of the common duct and of upper small intestine In four patients distention of the lower end of the esophagus produced pain similar to their clinical pain in the other five the chief difference was one of location

The striking similarity of pain induced from stimulation of (1) the common duct and upper small intestine and of (2) experimentally induced pain to that of biliary tract disease and pancreatitis emphasizes the difficulty in distinguishing between disturbances of these structures on the basis of pain symptoms alone Possibly the similarity may be due to the viscera having a common sensory supply the great splanchnic and lower thoracic sympathetic nerves

Significance of Bilirubin Partition in Hepatobiliary Diseases Because the diagnostic significance of partition of serum bilirubin into direct and indirect fractions in jaundice exclusive of the hemolytic form is not clearly established Fenton Schaffner Hans Popper (Northwestern Univ) and Frederick Steigmann[8] (Univ of Illinois) investigated this question in 279 jaundiced patients with verified diagnoses In addition 31 normal adults were used as controls

In evaluating the diagnostic value of the van den Bergh *reaction* initial values only were considered (*Table 1*) Patients with extrahepatic biliary obstruction had the highest concentration of both total and prompt reacting bilirubin whereas those with cirrhosis had the lowest values The ratios of prompt reacting to total bilirubin were similar in cirrhosis and infectious hepatitis on the one hand and in toxic hepatitis and obstructive jaundice on the other The significance of the difference between the means for prompt reacting and total bilirubin and prompt total bilirubin ratio was statistically expressed by t values (Table 2) Some of the differences in the bilirubin concentrations were statistically significant e g the difference in total bilirubin between cirrhosis and other forms of jaundice and in prompt reacting bilirubin between biliary obstruction and cirrhosis or infectious hepatitis There was no significant difference between biliary obstruction and toxic hepatitis or between toxic and infectious hepatitis The only significant difference in prompt total bilirubin ratio was

(8) Am J M Sc 219 307 315 M ch 1950

found between extrahepatic biliary obstruction and cirrhosis

Differences in total and prompt reacting bilirubin are of little *differential diagnostic value Only in cirrhosis are both* less elevated on the average than in the other conditions They reflect the stage rather than the etiology of jaundice Elevation of the prompt reacting fraction in subsiding jaundice indicates persistence of the disease

The most *significant change in serum bilirubin fractions* between normal serum and serum from jaundiced patients

TABLE 1—MEAN PROMPT REACTING AND TOTAL SERUM BILIRUBIN AND PROMPT TOTAL BILIRUBIN RATIOS IN 279 JAUNDICED PATIENTS AND 31 CONTROLS*

Diagnosis	No of Patients	Prompt Reacting Mg /100 Cc	Total Mg /100 Cc	Prompt Total Ratio
Normal	31	0.15	0.51	29.41
Cirrhosis	114	4.34	9.90	38.64
Infectious hepatitis	44	5.32	14.58	38.96
Toxic hepatitis	37	6.86	15.43	43.48
Extrahepatic biliary obstruction	84	8.16	18.72	43.45

* Initial determinations only

TABLE 2—T VALUES FOR DIFFERENCES IN MEANS OF PROMPT REACTING AND TOTAL SERUM BILIRUBIN AND PROMPT TOTAL BILIRUBIN RATIO BETWEEN VARIOUS ETIOLOGIC FORMS OF JAUNDICE*

	Prompt Reacting	Total	Prompt Total Ratio
Biliary obstruction—cirrhosis	4.67	5.60	2.69
Biliary obstruction—infectious hepatitis	3.20	1.96	1.73
Biliary obstruction—toxic hepatitis	0.96	1.15	0.01
Infectious hepatitis—cirrhosis	1.33	2.88	0.12
Toxic hepatitis—cirrhosis	2.00	2.06	1.79
Toxic hepatitis—infectious hepatitis	1.18	0.28	1.40

* A t value above 2.00 indicates a significant difference

exclusive of those with hemolytic jaundice is that the ratio of prompt reacting to total bilirubin is increased As jaundice becomes very deep the ratio tends to decrease although not *to the* level of serum from nonjaundiced patients These changes occur in both parenchymal and obstructive jaundice Differences in prompt total bilirubin ratio are therefore related to the level of total bilirubin rather than to the disease The amount of prompt reacting serum bilirubin depends on the degree of jaundice As jaundice develops the prompt reacting fraction increases more than the indirect When jaundice is established the rise of both fractions is fairly parallel

When bilirubinemia exceeds 40 mg /100 cc the increase of the indirect fraction is greater than that of the prompt reacting one

Comparison of the histologic picture of 153 liver biopsy specimens revealed no relation between presence or absence of jaundice and degree of liver cell damage There was a slight *significant correlation between presence of liver cell damage* and absolute values of prompt reacting and total bilirubin

These observations support the concept that bilirubin is changed from the indirect to the prompt reacting form in the Kupffer cells and is transmitted to liver cells for excretion The small amounts of prompt reacting bilirubin normally present in the blood are present because they have not been taken up by the liver cells In parenchymal jaundice liver cells are unable to accept all of the bilirubin and in obstructive jaundice they are unable to excrete it The result is a return of prompt reacting bilirubin to the blood and accumulation of bilirubin in Kupffer cells This accumulation impairs bilirubin uptake and results in subsequent indirect bilirubin increases

Limitations and Merits of Single Serum Sample Analysis in Differential Diagnosis of Jaundice are considered by F W Hoffbauer E D Rames and J K Meinert[9] (Univ of Minne sota) The biochemical procedures used on single serum sam ples *from 77* patients with extrahepatic biliary obstruction and 70 with parenchymal liver disease are listed in Table 1 The values presented in Table 2 indicate the anticipated re

TABLE 1—BIOCHEMICAL PROCEDURES USED

Procedure	Method	Normal Value
1 Serum bilirubin	Malloy & Evelyn as modified by Ducci & Watson	1 (prompt direct) 0 2 mg /100 cc (total direct + indirect) 1 0 mg /100 cc
2 Cephalin cholesterol flocculation	Hanger	A reading greater than 1 + at 24 hr may be considered abnormal
3 Thymol turbidity	Maclagan	0 4 units
4 Serum cholesterol (total)	Schoenheimer & Sperry	180 220 mg /100 cc
5 Serum cholesterol (esterified fraction)	Schoenheimer & Sperry	50 65% of total
6 Alkaline phosphatase	Bodansky	1 4 units/100 cc

(9) J Lab & Cl M d 34 1259 1278 S pt mbe 1949

sults assuming that the procedures would always yield results of differential diagnostic value Instances in which the actual results failed to conform with those listed in Table 2 are tabulated in Table 3

Certain characteristic biochemical responses occur fairly uniformly as a result of hepatic disease and bile duct obstruction Most patients with extrahepatic bile duct obstruction

TABLE 2—ANTICIPATED RESULTS IN BIOCHEMICAL TESTS USED BY AUTHORS

Type of Liver Disease	Cephalin Cholesterol (24 Hr Reading)	Thymol Turbidity (Maclagan)	Total Serum Cholesterol	Cholesterol Ester	Alkaline Phosphatase (Bodansky)
Extrahepatic obstruction	1+ or below	0-4 units	Above 225 mg /100 cc.	Above 50%	Above 10 units
Parenchymal liver disease	Above 1+	Above 4 units	Below 225 mg /100 cc	Below 50%	Below 10 units

TABLE 3—INSTANCES IN WHICH ACTUAL RESULTS FAILED TO CONFORM WITH ANTICIPATED RESULTS

Disease	Cases	Cephalin Cholesterol	Thymol Turbidity	Serum Cholesterol	Cholesterol Ester	Alkaline Phosphatase
Carcinoma	28	2	4	5	21	3
Common duct stone	39	2	1	12	11	12
Common duct stricture	10	0	1	3	2	1
Total	77	4	6	20	34	16
Cirrhosis	26	9	9	9	16	14
Hepatitis	31	5	6	11	10	8
Miscellaneous hepatic disease	13	10	9	2	6	4
Total	70	24	24	22	32	26

show elevated cholesterol and alkaline phosphatase *levels but* respond normally to thymol turbidity and cephalin cholesterol flocculation tests Many patients with jaundice due to diffuse liver disease exhibit biochemical changes of an opposite nature giving such tests a differential diagnostic value However some patients with parenchymal liver disease show cer

tain changes that closely parallel those seen in extrahepatic obstruction

This limitation of the use of the liver function test reflects a basic pathologic phenomenon Diffuse liver damage existing in hepatitis and cirrhosis may manifest itself with varying emphasis on hepatocellular or cholangiolar functional impairment The former is the classic type and resultant biochemical changes are quite characteristic and readily recognizable When the latter predominates the results of the tests may prove misleading from a differential diagnostic standpoint

[One interesting aspect of th contribution is a di cu sion of the minimum yet presumably adequate group of liver function test proposed in the past five years by different American investigators for differential diagnosis of jaundice As in the search for the Northwest Pa sage certain difficulties are always being encountered —Ed]

Quantitative Correlation of Morphologic Liver Changes and Clinical Tests was studied by Hans Popper Frederick Steigmann and Paul B Szanto[1] (Chicago) to determine (1) the statistical correlation between abnormalities in results of liver function tests and liver cell changes (2) which tests show the best correlation (3) if the number of tests with abnormal results is related to the degree of liver cell changes (4) if correlation between severity of liver cell damage and degree of functional impairment is related to the specific liver disease present and (5) which tests may be used as screening tests for presence of hepatic damage

Of 257 biopsy specimens 196 were obtained by Turkel needle aspiration and 61 by excision from patients with infectious and toxic hepatitis cirrhosis with and without jaundice extrahepatic biliary obstruction with and without infection and various gastrointestinal disorders for which laparotomy was performed

Hepatic tests were done at the time of or within two days before or after biopsy and were graded in abnormality from 0 to 3+ Liver cell changes were graded 0 to 3+ progressing from uniform appearance of cells and nuclei (0) to moderate variations with uniform cytoplasm (1) moderate irregularity of cells with nuclear abnormalities and/or changes in cytoplasm (2) and striking abnormalities (3)

The degree of structural liver cell damages of biopsy tissue was statistically correlated with the degree of abnormality

(1) Am J Cl P th 19 710 724 A g t 1949

in results of the series of liver function tests even though in individual cases no correlation existed Such correlation indicates only an association and does not establish that liver cell damage causes the test results Results of tests for total serum protein and cholesterol fecal urobilinogen nonprotein nitrogen prothrombin time and sedimentation rate had no significant association with degree of liver damage Urinary urobilinogen and alkaline phosphatase tests showed qualitative but not quantitative correlation with hepatic damage for biliary obstruction reduces urinary urobilinogen and elevates the alkaline phosphatase values independent of liver damage The degree of liver damage was significantly correlated with the serum bilirubin albumin globulin and flocculation tests Association with a decrease in albumin is explained by formation of albumin in liver cells Globulin increase is due to the mesenchymal reaction in many forms of hepatocellular injury except extrahepatic biliary obstruction without infection This accounts for the close correlation of cephalin flocculation and thymol turbidity with the degree of liver damage since both tests depend on elevation of globulins and decrease in albumin If secondary infection complicates extrahepatic biliary obstruction however these tests become positive

The greater the severity of liver damage the greater the number of positive liver tests independent of the physiologic basis of the test For screening purposes the cephalin flocculation and urinary urobilinogen tests are the most helpful since positive results indicate liver damage whereas negative results do not exclude it in presence of biliary obstruction

Differential Diagnosis of Jaundice Bernardo Sepulveda Horacio Jinich and Eduardo Barroso[2] review 125 cases studied between January 1947 and September 1948 There were 66 females and 59 males mostly adults For the purposes of this study only patients were classified as having one of three types of jaundice (1) prehepatic hemolytic or non hemolytic (2) intrahepatic parenchymal or cholangitic both acute and chronic (3) posthepatic benign or malignant without or with secondary hepatic lesion Diagnosis was confirmed by autopsy in 60 cases by liver biopsy in 33 and by operation in 14 (85 6 per cent altogether) in the other 18 the clinical picture and laboratory data did not leave any doubt as to diag

( ) Rev nv t g c on cl 1 169 189 J ly 1949

nosis In all patients a clinical history was taken and routine laboratory examinations were made liver function tests were repeated every 10 days in acute and every 20 days in chronic cases Special studies were made when indicated

Diagnosis of prehepatic jaundice generally was not difficult In diagnosis of intra or posthepatic jaundice there are useful and useless clinical laboratory and roentgenologic data Useful data are those which occur frequently or exclusively in one type of jaundice and rarely or not at all in another type The value of individual data must always be considered in connection with the entire picture Despite recent development of laboratory technics a good clinical history continues to serve as foundation for diagnosis With clinical data alone diagnosis was made in 70 per cent of these cases Roentgenologic and laboratory examinations are valuable aids when their results are judiciously interpreted 25 per cent of these cases were diagnosed with their use When these methods do not establish diagnosis liver biopsy may identify cholangitic or posthepatic jaundice with secondary liver lesion

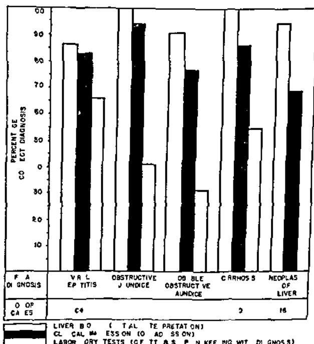
In cholangitic jaundice the symptomatic picture and some laboratory data are similar to those of benign posthepatic jaundice but the anatomicopathologic lesions predominate in the intrahepatic biliary canaliculi while the liver cells remain relatively intact There is no obstruction of the extrahepatic biliary passages This variety is rare It occurred in only 3 2 per cent of the 125 cases In practice it is found that these patients are operated on for obstruction of extrahepatic ducts When cholangitic jaundice becomes chronic it causes cholangitic cirrhosis which is similar to Hanot s cirrhosis

[Herewith is a glimpse into the attitude some of our friends below the border have toward the problem of jaundice from the diagnostic standpoint —Ed]

Needle Biopsy of Liver Experiences in Differential Diagnosis of Jaundice are reported by F G Weisbrod L Schiff E A Gall F P Cleveland and J R Berman[3] (Univ of Cincinnati) From 157 patients with jaundice 181 adequate liver biopsies were obtained Figure 123 shows that diagnosis based on biopsy was much more reliable than that based on the combined results of cephalin flocculation thymol turbidity and

(3) G t t I gy 14 56 72 J ry 1950

serum alkaline phosphatase determinations in the various forms of jaundice studied Errors in differentiating virus hepatitis from obstructive jaundice on the basis of needle biopsy are more likely to occur late in the course of virus hepatitis or in milder cases Morphologic changes in the first two weeks of obstructive jaundice may be wrongly ascribed



F g 123—Accu cy of n t l d g f s of j d e m de by l er b op y l cal xam n t n nd labo to y t t (C t y of W isb od F C f l Gast oe ter logy 14 56 72 Ja ary 1950)

to virus hepatitis Diagnostic efficiency improves as the per son performing the biopsies and the pathologist interpreting them become more experienced

[The conclusions of the authors of this instructive article are in strik ing agreement with those of Krarup (Acta med. Scandinav vol 136 supp 234 1949) whose authoritative and illuminating review in English I heartily recommend to all readers interested in this field —Ed]

↓ The following articles by Ricketts Palmer and their associates are two of an instructive series dealing with studies of serum proteins in vario s types of hepatic disease by means of the reliable Tiselius appa ratus Their findings are largely in agreement with those of other investi

gators notably those of Whitman Rossmiller and Lewis in untreated cases of portal cirrhosis (J Lab & Clin Med 35 167 180 February 1950) The beneficent results of modern methods of treatment are confirmed by their observations —Ed

Serum Proteins in Portal Cirrhosis under Medical Management Electrophoretic Studies Kenneth Sterling William E Ricketts Joseph B Kirsner and Walter L Palmer[4] (Univ of Chicago) carried out such studies on five patients with hepatic insufficiency and ascites during the course of medical management for periods up to 10 months and on five who had been severely ill with hepatic insufficiency but had clinically recovered with treatment and remained asymptomatic for over 2 years All patients were chronic alcoholics with proved portal cirrhosis

The patients in the first group initially had marked diminution of albumin fractions and elevation of gamma globulin fractions with somewhat less elevation of beta globulins During medical treatment serum proteins progressively approached normal coinciding with clinical improvement However *in two patients when clinical recovery was considered complete electrophoretic determinations still disclosed appre*ciable abnormalities in serum protein composition Determinations in the second group showed that the serum proteins may eventually become normal or nearly so in cases of long term recovery under medical management

Infusions of plasma were followed by increases in albumin beta and gamma globulin fractions and total proteins The immediate effects of administration of salt poor concentrated human albumin were striking elevation of albumin and depression of globulin fractions presumably due to dilution Shortly thereafter some decline of albumin and rise of gamma globulin and other globulin fractions occurred These changes may have resulted from decreased plasma volume as albumin left the circulation and subsequent concentration of globulin

Comparison of the alteration of serum proteins with results of various tests of hepatic function performed simultaneously failed to reveal any direct correlation

Electrophoretic Studies of Serum Proteins in Portal Cirrhosis William E Ricketts Kenneth Sterling Joseph B Kirsner and Walter L Palmer[5] (Univ of Chicago) investigated

(4) J Cl I t g t 28 1 36 1245 Septembe 1949
(5) G t oe t 1 gy 13 05 211 S pt mbe 1949

NORMAL SERUM

D B – Nearly normal pattern
Normal serum bilirubin
No clinical symptoms
Marked fibrosis and fatty infiltration histologically

I B Markedly abnormal pattern
Elevated serum bilirubin

A S – Markedly abnormal pattern
Elevated s rum bilirubin

M S – Extremely abnormal pattern Gamma globulin exce ds a.bumin
Elevated serum bilirubin

J B – Extremely abnormal pattern Unusual beta globulin peaks Gamma gl bulin exceeds albumin
Elev ted serum bilirubin

F g 124—P tal c h w th t a te (p t ts D B and I B) nd p t l ho w th t (p ts A. S M S a d J B) Alb m n p d t d by A d the glob l by G k l tt U lab l d peak a t ton y an m l a b d d t g ad t f b ff lt (C u t y f R k tt W E t l Ga t oent ol gy 13 205 211 S pt mb 1949)

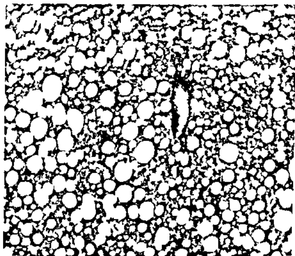
the relation between electrophoretic pattern and clinical findings in 14 proved cases of portal cirrhosis Electrophoretic runs were performed with standard apparatus and technic Simultaneously tests were done for serum bilirubin total proteins albumin and globulin alkaline phosphatase bromosulfalein retention thymol turbidity and cephalin flocculation All determinations were also made on a control group of 10 nor

mal subjects The 14 patients with portal cirrhosis were divided into 7 with ascites and 7 without clinical evidence of ascites In the latter group three patients without clinical symptoms of liver disease were regarded as having latent portal cirrhosis histologically verified All tests were performed before or very early in the course of medical management

Electrophoretic analyses in the 14 cases of portal cirrhosis revealed pronounced deviations from normal composition In both per cent composition and absolute amounts there were diminutions of the albumin fractions and elevations of gamma globulin to double or triple normal values In four of seven cases without ascites gamma globulin exceeded albumin A less frequent abnormal finding was elevation of beta globulin (Fig 124) In two cases beta globulin was almost as high as gamma globulin with bizarre double peaks in one As expected patients with ascites had lower albumin values than those without although alterations in serum protein composition were similar in both groups The three patients with latent portal cirrhosis had serum protein compositions close to normal There was no direct correlation between alterations of serum proteins and results of various hepatic function tests

Liver Damage Produced by Feeding Alcohol or Sugar and Its Prevention by Choline C H Best W Stanley Hartroft C C Lucas and Jessie H Ridout[7] (Univ of Toronto) studied 188 male rats fed a basal ration as adequate as possible in all its dietary components except lipotropic factors A 15 per cent aqueous solution of purified ethyl alcohol was given in place of drinking water to four groups of rats for 177 days In another four groups caloric equivalence was achieved by adding powdered sucrose instead of alcohol to the diet Hepatic lesions were found in the animals receiving dietary supplements of sucrose which were so similar in character and extent to those produced by an isocaloric amount of alcohol that they were indistinguishable In the rats consuming alcohol fatty livers developed that contained an average total lipid content of 20 per cent (Fig 125) the livers of those fed sucrose contained 26 per cent total lipids Of the rats that survived the experimental period half of those drinking alcohol

(7) B t M J 2 1001 1006 N v 5 1949





F 1 5 (top) —F tty h ng (4 pl s) n l e f at f d b l d t d g ve 15 per t al ob l n place f d k g water Pa ffi s ct o a oc r l ne bl e a d o a ge L × 80

F g 126 (bottom) —W ll d fi d fib s of l e f t f d basal d t and ga Paraffi sect on a oc m e a l e bl nd ora ge G × 80

(Courte y f Best C H t al B t M J 2 1001 1006 No 5 1949)

had hepatic fibrosis whereas only 2 of 28 control survivors showed this change Of the nine survivors fed sucrose iso calorically the livers of seven showed fibrosis (Fig 126)

Rats maintained on the basal diet alone grew well showed no liver fibrosis and had an average total liver lipid content of 9 3 per cent In animals receiving lipotropic supplements such as choline chloride or methionine whether or not alcohol or extra sugar had been consumed no abnormalities were de tected on gross microscopic or chemical examination of the livers

The experiments provided no more evidence of a specific toxic effect of pure ethyl alcohol on liver cells than of one due to sugar Since the usual vitamins were present in the basal diet in more than adequate amounts and since the lesions were prevented by extra choline it may be concluded that the hepatic changes associated with ingestion of pure ethyl alco hol were due to induced choline deficiency

Pathology of Subchronic Atrophy of Liver Comparison with Laennec s Cirrhosis Mogens Bjorneboe and Flemming Raaschou[8] (Copenhagen) report that almost all of 108 pa tients with subchronic atrophy (subacute yellow atrophy) of the liver were women whereas 33 of those with Laennec s cirrhosis were women and 43 men In general the liver in subchronic atrophy is smaller than in cirrhosis a difference which may explain the greater frequency of hepatic coma in the former There were five instances of primary carcinoma and four of hepatoma among patients with cirrhosis but neither condition occurred in those with atrophy About 90 per cent of those with subchronic atrophy and only 41 per cent of those with cirrhosis died with icterus Although portal hypertension is pronounced in cirrhosis the incidence of splenomegaly did not differ greatly in the two groups Ascites and hydrothorax were more common in those with subchronic atrophy probably because of the lower colloidal osmotic pres sure Esophageal varices were more frequent in those with cirrhosis

Punch biopsy specimens from eight patients with sub chronic atrophy showed changes indistinguishable from those of severe acute hepatitis A hemorrhagic tendency was pres ent in 64 8 per cent of patients with subchronic atrophy and

(8) A h I t M d 84 933 957 Dec mb 1949

in 16 per cent of those with cirrhosis Gastric ulcer occurred in 10 2 per cent of those with atrophy and in 2 6 per cent of those with cirrhosis

There is a greater degree of reduction of liver parenchyma in subacute atrophy than in cirrhosis Clinically a greater frequency of symptoms of loss of hepatic function coincides with this change

Chronic Liver Disease Following Infectious Hepatitis Cirrhosis of Liver Henry G Kunkel and Daniel H Labby[9] (Rockefeller Inst) report development of clinical evidence of severe cirrhosis two to six years after an attack of infectious hepatitis in five patients four service men and one girl aged 18 Though infectious hepatitis can never be diagnosed with absolute certainty these selected patients had a sudden onset of jaundice associated with gastrointestinal symptoms when they were young and in good health A history of contact was obtained in two and the others were service men whose illness appeared to be part of the wartime epidemic of infectious hepatitis

In the histories of these patients certain factors may account for deviation of infectious hepatitis from its usual benign course In two patients activity during the acute stage was important They continued wartime duties despite severe jaundice A second factor in the development of cirrhosis in these two might have been age both were over 30 which is considerably above the average age for servicemen who contracted infectious hepatitis A third factor of importance in two of the other three patients was severe bacterial infection complicating infectious hepatitis These observations suggest that when cirrhosis of the liver develops after infectious hepatitis there are almost always complicating factors

The clinical picture of cirrhosis was quite variable in the five patients The course differed from that usually seen in Laennec s cirrhosis in that the disease was progressive and not materially affected by therapy In two patients the dominant manifestation was frequent esophageal hemorrhages In all the primary aberrations in liver function were those related to protein metabolism and serum albumin concentration was depressed early in the course The pronounced abnor

(9) A Int Med 3 433 450 Ma h 1950

mality in the globulin fraction of the serum was further evidence of primary cellular damage to the liver Physical examination revealed many spider angiomas in two patients and decided liver enlargement in four All had splenomegaly and four showed leukopenia and anemia Late manifestations of the disease resembled those described in the past under Banti s syndrome The most characteristic feature in the clinical course was the progressive nature of the disease once cirrhosis was established

The characteristic lesion was an irregular nodular hyperplasia of liver cells between broad areas of contracted reticulum and fibrous tissue The cirrhosis closely resembled the lesion described by Mallory and called toxic cirrhosis or healed acute yellow atrophy In four patients the picture differed from that seen in classic Laennec s cirrhosis

[Modern diagnostic technics particularly aspiration liver biop y a well as evidence gleaned from autopsies to date leave no doubt that acute infectious hepatitis may progress to one of the various forms of cirrho i postnecrotic, nodular or even the Laennec type The only question that remains is how often such complication occurs This challenging problem has been taken up for solution by the National Research Council —Ed.]

Central Nervous System in Hepatic Disease A B Baker[1] (Univ of Minnesota) studied the central nervous system in 18 cases of acute subacute and chronic liver disease and found extensive changes in 8 Alterations involved both gray and white matter and were found in all regions of the brain Most prominent were nerve cell damage and widespread areas of demyelination which were predominantly perivascular and at times extensive Compound granular corpuscles were never present in involved regions Nerve cells were irregularly damaged and showed chromatolysis fragmentation and loss of tinctorial properties

It is apparent that there may be a definite relation between the brain lesions and hepatic damage The possibility must be considered that the factors which cause liver disease may also produce concomitant brain damage However the evidence obtained in this series and a review of the literature suggest that liver damage enables some endogenous toxin to reach the brain producing changes

‡ The following three articles are concerned with an important, still incompletely solved problem of hepatic disease or dysfunction, namely the

(1) J Neuropath & Exper Neurol 8:283-294 July 1949

causative factors giving rise to hemorrhagic diathesis Of interest are the observations on the highly probable role of increased capillary fragility and other possible factors —Ed

Thrombopenia and Increased Capillary Fragility in Hepatic Disease Hypoprothrombinemia is responsible for the hemorrhagic tendency in obstructive jaundice but many investigators do not consider it the sole cause of bleeding in parenchymal liver disease Because of the many patients seen

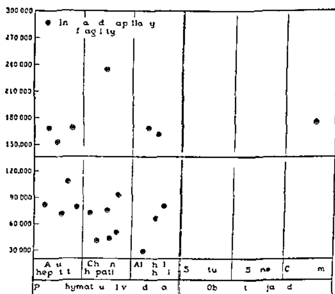


Fig 127 —M th mb yt nt hep t d s h wn n t al l of fig es t left (Cou t y f Wh t ll F B Jr a d S ell A M J A M A 140 1071 1076 J ly 30 1949)

with the various residua of hepatitis and the apparent increase of atrophic cirrhosis Frank B Whitesell Jr (Mayo Found) and Albert M Snell (Mayo Clinic) studied the relation of thrombopenia and increased capillary fragility to the coagulation defects in hepatic disease Clinical data were gathered on 70 patients with hepatic disease and 20 controls with unrelated conditions A petechial index of less than 23 determined by the Rumpel Leede technic and a mean thrombocyte count of more than 137 000 were accepted as normal Figure 127 shows

(2) J A M A 140 1071 10 6 J ly 30 1949

the distribution of cases according to the type of lesion with the respective thrombocyte counts Thrombopenia was found in only 4 of 29 cases of extrahepatic obstructive jaundice and increased capillary fragility in 1 Thrombopenia and/or increased capillary fragility was found in 37 of 41 cases of parenchymal liver disease The data presented applies primarily to these 37 cases

Patients with acute hepatitis had decided icterus and a high serum bilirubin level whereas those with chronic hepatitis had minimal icterus and a low bilirubin level Most patients with alcoholic cirrhosis had little or no icterus There was no apparent correlation between jaundice and the thrombocyte count or petechial index The predominant complaint of these patients increased tendency to bleed was usually related to severe parenchymal liver damage No correlation was evident between thrombopenia and increased capillary fragility and the prothrombin time Thrombopenia often seemed responsible for bleeding when the prothrombin time was at or near normal limits particularly when the thrombocyte count was 50 000 or less In several surgical patients bleeding on this basis proved serious and difficult to control Physical examination revealed enlarged spleens in 30 per cent of the patients with acute hepatitis in 43 per cent with chronic hepatitis and in 29 per cent with alcoholic cirrhosis

In many cases plasma protein values fell within normal limits Invariably such values were due to an increase in the globulin fraction with either equalization or reversal of the albumin globulin ratio In most instances further study revealed elevated gamma globulin serum values When the sulfobromophthalein test was done on nonicteric patients with thrombocyte and capillary defects all had more than 12 per cent dye retention at the end of one hour Cephalin cholesterol flocculation tests were strongly positive for 88 per cent of the patients thymol turbidity was increased in 64 per cent Red and white cell counts and differential smears revealed nothing but mild secondary anemia in a third of the patients Sternal marrow studies showed active marrows and an adequate number of megakaryocytes In general bleeding time was prolonged with normal or slightly prolonged clotting time and poor clot retraction In the four cases presented needle punch biopsy of the liver revealed subacute hepatitis

chronic atrophy of the liver postnecrotic cirrhosis and portal cirrhosis respectively

The authors conclude that thrombocyte and capillary defects are extremely common in parenchymal liver disease that there is some correlation between these defects and an abnormal state of the serum colloids notably a great increase in gamma globulin, and that it is important to differentiate thrombocytic and capillary defects due to hepatic disease from true idiopathic thrombopenia A complete evaluation of hepatic function supplemented by liver biopsy if necessary should be made in all cases of idiopathic thrombopenia before considering splenectomy When thrombopenia and increased capillary fragility occur surgery is complicated by the risk of hemorrhage in addition to that due to any existing deficiency of prothrombin There is also danger of precipitation of terminal hepatic insufficiency

Relative Importance of Plasmatic and Vascular Factors of Hemostasis in Pathogenesis of Hemorrhagic Diathesis of *Liver Dysfunction* *About 15 per cent of patients with liver* dysfunction present spontaneous hemorrhagic symptoms due to abnormalities of some plasmatic and vascular factors of hemostasis To determine relative individual importance of these factors Mario Stefanini and Emilio Petrillo[3] studied 30 patients with proved liver dysfunction who manifested concomitant hemorrhagic symptoms In all hematogenic conditions were carefully studied

It was concluded that hypofibrinogenemia almost a constant sign of liver dysfunction was never per se responsible for hemorrhagic manifestations The critical level of fibrinogen concentration below which hemorrhagic symptoms will appear *is very low probably reached only in cases of extreme* liver dysfunction It was established by Pinniger and Prunty to be equal to 60 mg /100 cc plasma The authors study confirmed these findings Prothrombin activity was below 20 per cent of normal (the critical level for occurrence of hemorrhages) in 23 3 per cent of cases and below 50 per cent in 26 7 per cent In all cases increased capillary fragility accompanied hypoprothrombinemia In the other 50 per cent increased capillary fragility alone was responsible for hemorrhagic manifestations since prothrombin activity and fibrinogen level

(3) Acta med Scand na 134 139 145 1949

were both above critical levels Since hemorrhages do not seem to occur in cases in which prothrombin activity is below the critical level but capillary resistance is normal a serious de fect of the plasmatic factors of the coagulation mechanism will probably not give rise to spontaneous hemorrhages when capillary resistance is normal Hypoprothrombinemia and in creased capillary fragility are associated factors in the oc currence of hemorrhagic manifestations of liver dysfunction in 50 per cent of cases This suggests a common underlying mechanism possibly a deficiency in utilization of vitamin K by a damaged liver

Hemorrhagic Tendency in Sclerosing Hepatopathies Jose Baez Villaseñor and Jorge Medina Zamitiz[4] (Hosp de Enfer medades de la Nutricion) studied the frequency and type of hemorrhagic manifestations in 60 patients with various types of hepatic cirrhosis in 49 clinical diagnosis was confirmed by histologic examination The following tests were carried out bleeding time tourniquet prothrombin time clotting time of oxalated and recalcified plasma platelet count and clot re traction

Hemorrhages were observed in 33 cases gastrointestinal hemorrhage in 18 epistaxis in 14 cutaneous bleeding in 6 and buccal bleeding in 4

In gastrointestinal hemorrhage rupture of esophageal varices due to portal hypertension was the most important cause Hypoprothrombinemia was frequently associated and could have been a contributory cause Only in two cases was gastrointestinal hemorrhage entirely due to hypoprothrom binemia in both the blood came from gastric extravasation Gastrointestinal bleeding caused by disturbances of hemo stasis other than hypoprothrombinemia was not observed

In nasal cutaneous and buccal bleeding the most frequent etiologic factor was hypoprothrombinemia usually severe to which was added a disturbance in the capillary factor of hemostasis in 16 6 per cent of the cases as shown by the pro longed bleeding time The latter was the only alteration in 6 per cent of the patients

Hypoprothrombinemia caused bleeding only if it was severe In those cases there was also pronounced hepatic in sufficiency Thrombocytopenia was observed in 6 per cent of

(4) R t g ion l 2 81 91 J n ry 1950

the cases and was the principal factor in the production of epistaxis bleeding from the gums and ecchymosis It was always a feature of a hypersplenism syndrome

The authors point out and discuss both normal and abnormal values and compare them to those encountered by other investigators

Improvement of Active Liver Cirrhosis in Patients Maintained with Amino Acids Intravenously as Source of Protein and Lipotropic Substances To determine whether intravenous administration of protein hydrolysates for hepatic insufficiency is desirable or is contraindicated because of delayed deaminization and resultant high incidence of reactions Richard D Eckhardt William W Faloon and Charles S Davidson[5] (Harvard Univ) studied clinical tolerance metabolism excretion and therapeutic value of protein hydrolysates in four patients with cirrhosis A 10 per cent solution of amino acids was used as the sole source of nitrogen and lipotropic substances

The basal diet adequate in calories but devoid of protein was ingested at regular meal hours Protein for the day 500 1 000 cc of the amino acid solution was supplied in one rapid intravenous injection one hour after breakfast Addition of 50 100 Gm hypertonic glucose to the infusion helped to achieve maximal utilization of amino acids by simultaneous provision of adequate carbohydrate and protein

Amino acids administered intravenously were as well tolerated by these patients as by normal persons Few reactions followed rapid and repeated infusions of protein substances Metabolism of the amino acids was normal shown by positive nitrogen balance and normal blood amino acid values after infusion Amino acids given parenterally were excreted in a normal manner even in the presence of severe liver damage All patients improved and showed progressive reduction of serum and urine bilirubin and of jaundice Hepatosplenomegaly was reduced in two patients and biopsy showed distinct improvement of the liver structure in one patient

It is not suggested that patients with liver disease receive a *daily* protein free diet with amino acids given intravenously as the sole source of nitrogen and lipotropic substances Therapy in hepatic disease is still fundamentally based on an ade

(5) J Clin. I t gat on 28 603 614 J ly 1949

quate nutritious diet. However when adequate food intake cannot be maintained intravenous administration of amino acids is indicated.

Primary Biliary Cirrhosis. The possible etiology of biliary cirrhosis is given in the following classification used by Karsner (1) Types due to extrahepatic obstruction of large bile ducts are (a) cholestatic and (b) cholangitic. (2) Types due to intrahepatic obstruction of finer bile channels are (a) cholangitic, (b) cholangiolitic, (c) xanthomatous and (d) zooparasitic. James A. Dauphinee and Jonathan C Sinclair[4] (Toronto) discuss 10 cases belonging to group 2 in which the extrahepatic biliary channels are unobstructed and in which a possible mechanical obstruction is in the smallest interlobular branches of the biliary tree. This diffuse process involving the whole intrahepatic biliary tract leads to pronounced enlargement of the liver and spleen and to persistent jaundice. Although relatively rare, this condition of primary biliary cirrhosis is important because patients who have it are often thought to have extrahepatic obstruction and are therefore needlessly subjected to surgery.

In these 10 cases there was mild to severe visible jaundice associated with itching of varying degrees of severity. True, colicky pain was present in only one case. Although mild fever was common, high temperatures were uncommon. Multiple xanthomatosis was prominent in three cases and true spider telangiectasis in two. There was a large firm liver and a readily palpable spleen in all patients. Late ascites was encountered in four cases. Severe hematemesis occurred in one case and to a lesser degree in another. Laboratory examinations showed elevation of the direct reacting serum bilirubin in all 10 cases, definite urobilinogenuria in 9, hypercholesteremia in 7 and hyperphosphatemia in 10. A mild lowering of serum albumin values occurred in four and moderate or striking elevation of serum globulin values in five. Galactose tolerance test was positive in only two cases. Microscopically the liver showed an inflammatory process characterized by round cell infiltration and increasing fibrosis in and about the portal spaces and obstruction and obliteration of the fine, interlobular bile capillaries.

The symptom complex of primary biliary cirrhosis is so

[4] Canad. M. A. J. 61 1-6, July 1949

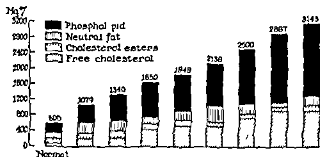
similar to that of an obstructive lesion that a diagnosis of extrahepatic obstruction is easily made However lack of a suggestive history relatively mild jaundice at first large liver without gross irregularities palpable spleen and some times parenchymal cell involvement suggest an intrahepatic lesion and often permit the correct diagnosis to be made on clinical grounds alone

Relationship between Serum Lipids and Skin Xanthomas in 18 Patients with Primary Biliary Cirrhosis is clarified by Edward H Ahrens Jr and Henry G Kunkel[7] (Rockefeller Inst) In seven patients the xanthomas were generalized large tuberous and flat in eight the distribution was localized to the eyelids (xanthelasma) Xanthomas have not yet developed in three patients Typical patterns of serum lipids in eight patients with primary biliary cirrhosis are presented in Figure 128 These patterns show a marked similarity irrespective of total lipid concentrations or presence or absence of xanthomas Preponderance of phospholipids was noted at all levels of total lipid concentration The rise in free cholesterol concentration was evident but not as pronounced as the phospholipid increase Cholesterol ester concentration was normal or slightly elevated The ratio of free to total cholesterol was greatly elevated in all patients because of the characteristic increase in the free form Neutral fat levels were moderately elevated in all patients except during periods of malnourishment on low fat diets or terminally Every fasting serum seen in this series of patients was clear Figure 129 shows typical lipid patterns in other hyperlipemic conditions and demonstrates the unique pattern of primary biliary cirrhosis All high lipid serums except those found in biliary obstruction are lipemic

All patients with prolonged elevation of total serum lipids above 2000 mg per cent developed severe generalized skin xanthomas Those with total lipid levels below 1 300 mg per cent showed no xanthomas whereas those in the intermediate range have xanthelasma For the first time disappearance of skin xanthomas has been noted coincident with a fall in total serum lipids This occurred in four of seven patients with severe xanthomas Xanthomas were absent in patients who showed the least jaundice and elevation of total lipids Labo-

(7) J Cl n I e t gat on 28 1565 1574 (pt 2) N mbe 1949

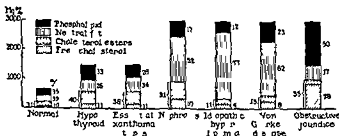
ratory evidence of the degree of biliary obstruction showed *striking spontaneous variability and complete obstruction* was not found in a single patient The largest groups of pa



Jaundice	0	2½	1¼	1	3½	3½	6	3	2¼
Xanthelasma	0	0	4	0	1¼	1¾	3	2	¼
Severe xanthomata	0	0	0	0	1½	1¾	5	2	¾

Durat on years

F g 128 —S rum l p d patterns n ght pat t w th p im ry b l ry h (C rt y f Ah E H J nd K nk l H G J Cl n In t ga ion 8 1565 1574 (pt 2) Nov mb 1949)



F g 1 9 —R p es tat l p d p tt a c hyp l p m d tion Hypo thy d p c l l t d f m dat f G ld M a d P ter J Cl n I t g 18 739 755 Nov mb 1939 (Co rte y f Ah n E H J and Ku k l H G J Cl I t g t o 8 1565 1574 (pt 2) N mb 1949)

tients remained arrested in the prexanthomatous phase of the disease and had lipid levels which never exceeded 1 800 mg per cent

[An important contribution to our increasing knowledge of an in triguing di ease especially from the standpoint of a level of tota serum l pids critical for the appearance of xanthom s Moreover the ev dence presented for a prexanthomatous stage in development of the full blo vn

disease will in all likelihood stand The investigators observations on the efficacy or rather the lack of it of various dietetic and other therapeutic measures to influence the lipid level of the serum are to the point Xanthomas of diabetic origin have long been known to disappear after control of diabetes by diet and insulin Similar research in this disorder seems appropriate —Ed]

Nutritional Disease of Liver I J Wood H W Garlick R Motteram S Weiden A Moore M Mackay and C N Turner[8] studied 18 patients with nutritional disease of the liver by clinical observation biochemical tests and aspiration biopsies of the liver Etiology of the condition was established by comprehensive dietetic history obtained from patients relatives and associates Malnutrition was most frequently associated with alcoholism

Clinical findings were increasing lassitude weakness and impairment of mentality Appetite was poor and nausea frequent Jaundice was slight or absent in most cases Hematemesis occasionally occurred The liver was usually enlarged and tender especially during acute relapses Vitamin deficiency lesions frequently coexisted

In early cases biochemical studies showed liver functions to be normal Slight jaundice was not uncommon Only in severe relapses was there considerable rise in serum bilirubin content When portal cirrhosis was established there was usually a positive cephalin flocculation test impaired hippuric acid excretion an increase in urobilinogen in the urine a slightly raised or normal alkaline or phosphatase level and a reversal of the albumin globulin ratio In cases of external obstruction the cephalin flocculation test was negative or weakly positive and alkaline phosphatase level high In cases of chronic infectious hepatitis the cephalin flocculation test was strongly positive albumin globulin ratio reversed and alkaline phosphatase level only moderately elevated Aspiration biopsies of the liver provided a means for observing the various stages of the disease and for establishing diagnosis

Treatment consisted of removal of toxic substances correction of dietetic habits and a diet rich in protein and vitamins Choline chloride may be given in doses of 9 Gm a day Intercurrent infections must be treated

If treatment can be maintained early nutritional disease of the liver may be cured and the downward trend of severe advanced disease may at least be retarded

(8) M J Australia 1 541 547 Apr 23 1949

Primary Malignancy of Liver is discussed by Irving B Brick[9] (Georgetown Univ) who presents two brief case histories Incidence of liver carcinoma varies in different parts of the world In the adult Bantu native this carcinoma is the most common This is of interest because in these people malnutrition fatty infiltration of the liver and portal cirrhosis are common Liver carcinoma is frequently encountered in India Japan and China Some of these people continue to be susceptible even when they change the location of their habitation

The two main varieties are hepatoma and cholangioma The former occurs three times more frequently than the latter Hepatoma arises from liver cells whereas cholangioma originates from bile duct epithelium Cirrhosis can usually be found in some portion of the liver In Asiatics especially Chinese liver fluke infiltration with subsequent development of cirrhosis is common and may partly explain the frequency of liver carcinomas Constant use of butter yellow (an azo dye) has been advanced as the explanation of liver carcinoma in the Japanese The major metastases of these tumors are via the blood stream rather than the lymphatics

Important clinical findings are abdominal pain weight loss weakness jaundice edema of the extremities hepatomegaly ascites and anemia The usual course is short being less than five months in 86 per cent of reported cases The clinical picture may simulate cirrhosis but cancer should be suspected if the course is rapidly downhill X rays which show an elevated right diaphragm with bulges but without pleural reaction or a large right upper quadrant mass may be of diagnostic aid Liver function tests generally indicate hepatocellular damage The simplest least expensive method of diagnosis is needle biopsy of the liver by which frequency of diagnosis may be increased Therapeutic measures are rarely helpful in increasing duration of life

On Alleged Adiposity of Gallstone Patients Using Broca s formula that the weight in kilograms of a fullgrown person equals the height in centimeters — 100 E Schiødt[1] (Aalborg Denmark) found that the average weight of 19 men with gall stones corresponded exactly to this standard In 43 women

(9) Am P ct 1 475 479 M y 1950
(1) A ta m d, S d (pp 234) 136 299 303 1949

with gallstones weight was increased an average of 2 8 per cent In 19 men and 43 women with medical diseases excluding cholelithiasis average deviation was — 5 5 per cent for men and + 3 6 per cent for women The two groups were practically identical as to weight and the distribution in both gave a fairly regular gaussian curve Weights in both groups were independent of age

A group of 208 men and 215 women with mental diseases showed an average deviation of — 3 2 per cent for men and of + 4 6 per cent for women

Apparently medical patients with cholelithiasis do not differ in weight from patients with other medical diseases or control patients

On Reoperation for Choledocholithiasis Experience from and Comments on 34 Operated Cases Erik Millbourn[2] (Univ of Lund) reports that in 12 cases findings were negative at reoperation but in 22 stones were found in the common bile duct The stones were unquestionably overlooked at the primary operation in 11 cases probably overlooked at the primary operation in 4 probably freshly formed after the initial operation in 5 and unquestionably freshly formed in 2 Calculi were probably responsible for postoperative symptoms in six cases and were probably passed spontaneously to the duodenum immediately before reoperation in four and after reoperation in two Postoperative symptoms were due to cholangitis in one biliary stricture in one dyskinesia in two and disease resembling cholelithiasis in two Nonabsorbable suture material should not be used adjacent to the bile ducts for it may migrate into them and be the nidus for subsequent calculus formation

Reoperation for postoperative biliary distress must often be postponed until jaundice attacks of cholangitis or increased diastase content of blood or urine are so pronounced as to obviate any doubt as to the presence of calculi Diagnosis may be difficult because of the long latent period which may follow the initial operation and occurrence of signs and symptoms atypical of biliary colic

To avoid overlooking calculi in the deep bile ducts cholangiographic examination should be performed during operation If choledochotomy is established it should be performed

(2) A ta ch S a d 99 285 312 1950

postoperatively also Cholangiography is especially important if reoperation is contemplated If stones are few small and movable reoperation should be postponed until several months or years after the primary procedure If cholangiography at reoperation discloses that calculi have not been overlooked the patient s prospects of becoming symptom free are good

The primary mortality in 34 reoperations was 9 per cent

[The author properly stresses the difficulty of diagnosis in these late painful recurrences after operation for bona fide cholelith c disease Although the series investigated was small (34 patients) the presence of duct stones in a little over two thirds of the patients at a secondary operation perhaps represents a higher average than is usually reported It is not unusual for even the expert surgeon to overlook stones in the intrahepatic and common ducts at operation although routine use of the scoop and/or sound reduces the incidence However the increasing use of cholangiography after operation further minimizes this possibility It is unfortunate that one cannot resort to this useful procedure once the operative wound is healed The role of formation of new duct stones in the absence of the gallbladder has not received much consideration in the past Wilkinson (S Clin North America 28 587 591 June 1948) has emphasized the diagnostic usefulness of duodenal drainage in these circumstances —Ed]

External Pancreatic Secretion as Measured by Secretin Test in Patients with Idiopathic Steatorrhea (Nontropical Sprue) Manfred W Comfort George R Dornberger Eric E Wollaeger and Marschelle H Power[3] (Mayo Clinic) analyzed duodenal contents collected from 13 patients with idiopathic steatorrhea before and after stimulation with secretin Values for volume and bicarbonate and enzyme contents were noted The mean total volume for the 40 minutes after stimulation was somewhat greater than the corresponding normal value but the difference was not statistically significant In determination of total bicarbonate values the mean fell within normal limits That for total enzymes was within or above normal limits

The normalcy of function as measured by the secretin test probably indicates that pancreatic dysfunction had no part in these 13 cases of idiopathic steatorrhea Results previously reported showed impairment of external pancreatic function in steatorrhea due to pancreatic disease The secretin test therefore might be used in differentiation of idiopathic steatorrhea from that caused by pancreatitis However it is felt that such differential diagnosis may be better accomplished

(3) G at oe t l gy 13 135 140 A gu t 1949

by using clinical data in conjunction with less time consum ing laboratory procedures

Etiology, Pathology, Diagnosis and Treatment of Acute Pancreatitis Review of 110 Cases is presented by R A Russell Taylor[4] Despite many studies the genesis of acute hem orrhagic pancreatitis is not yet adequately explained Obstruc tion which allows reflux of bile along the pancreatic duct or infection of the pancreas from a distant focus by the blood stream may be significant factors Acute pancreatitis occurs most commonly between ages 40 and 60 with about equal sex distribution There seems to be a definite association with obesity cholecystitis and cholelithiasis

When the pancreas is infected at operation it must be re membered that acute necrosis may be present although mac roscopically the pancreas may appear normal On the other hand the pancreas may appear hemorrhagic gangrenous or suppurative Although fat necrosis is the most distinctive fea ture of pancreatitis it is not pathognomonic for it may occur with perforation of an ulcer of the second portion of the duo denum

Acute pancreatitis should be suspected in the stout elderly patient with a previous history of indigestion who has an attack of severe upper abdominal pain in association with decided epigastric tenderness without muscular rigidity upper abdominal distention flatulence frequent vomiting and a rapid weak pulse If the first specimen of urine contains 100 or more units of diastase and if the serum calcium is below 9 mg /100 cc the diagnosis is more likely

In 41 patients the following conservative treatment was given with a mortality of 26 8 per cent

TREATMENT —Whole blood transfusions and intravenous saline and glucose solutions are given as indicated Glucose should be used sparingly because an elevated glucose level may cau e an increased flow of pancreatic juices Since morphine may cause contraction of the sphincter of Oddi with resulting rise in biliary and pancreatic pressure its use *for pain should be avoided For this purpose in* halations of amyl nitrite nitroglycerin tablets papaverine or atro pine may be of value becau e of their antispasmodic effect Atropine sulfate may be given in doses of 1/50 gr every 6 hours for 24 hours A 10 per cent solution of calcium gluconate may be given intra venously in 10 cc doses to supply calcium for the formation of cal cium soap in situ without depletion of serum calcium Intravenous

(4) An Roy Coll S g on F gl d S 13 39 O tobe 1949

therapy is continued for three or four days and nothing should be given by mouth to inhibit pancreatic activity Oral food intake should be resumed carefully with easily assimilable carbohydrates Fat is not permissible for several weeks and meat is forbidden since protein intake must be limited

In 69 cases operation was performed with a mortality of 40 6 per cent Indications for operation are persistent fever or development of fever along with other abdominal signs spreading peritonitis pancreatic necrosis distention of the lesser peritoneal cavity enlarged gallbladder jaundice no response to conservative treatment uncertain diagnosis traumatic pancreatitis with involvement of other organs associated biliary tract disease retroperitoneal involvement as shown by discoloration in the loins and pseudocysts or fistulas of the pancreas Postoperative complications usually associated with acute pancreatitis include reopening of the surgical incision thrombosis of splenic and mesenteric veins pancreatic insufficiency diabetes mellitus and pseudocysts or fistulas of the pancreas

Acute Pancreatitis Pathways of Enzymes into Blood Stream Acute trauma or inflammation of the pancreas and major salivary glands in man particularly the pancreas is associated with an elevation of blood amylase concentration John M Howard A Krehl Smith and J Joseph Peters[5] (Univ of Pennsylvania) produced acute pancreatitis experimentally to determine whether or not the inju ed pancreas is the source of additional serum amylase and by what pathway the enzyme reaches the blood

PROCEDURE—In each of 10 dogs two episodes of acute pancreatitis were produced within two weeks Pancreatitis was initially produced by ligation and dissection of the pancreatic ducts thereby preventing enzyme passage into the gastrointestinal tract At the end of the first operation the thoracic duct was ligated excluding lymphatic tran portation of enzymes The second episode was produced by injection of sterile bile into the pancreatic ducts Pancreatic enzymes thus had access to the body only through the blood

Blood was drawn from the femoral vein and artery for amylase determinations immediately before and after anesthetization and from the aorta pancreatic vein and artery before and after pancreatic duct ligation Urine specimens were obtained at 30 minute intervals Blood and urine collections were repeated during the second operation

Before trauma amylase levels in pancreatic arterial and

(5) S g y 26 161 166 A g t 1949

venous blood serum were equal After production of pan creatitis amylase concentrations increased rapidly and venous serum levels were higher than arterial The absence of amylase in the gastrointestinal tract and the obstruction of thoracic and pancreatic ducts proved at autopsy together with the high concentration in the venous blood serum demon strate that the enzyme is released from the traumatized pan creatic cells into the surrounding tissue and absorbed directly into the blood stream

It is suggested that other enzymes trypsin and lipase may be concentrated in the pancreatoportal system after pancreatic damage and that one or more of these enzymes in high con centration may be hepatotoxic The toxemia of pancreatitis may be due in part to hepatic damage caused by these en zymes

[Apparently none of the current theories of the genesis of acute pan creatitis adequately explains the mechanism of production One authority has pointed out that the solution of this problem is more likely to be found in the experimental laboratory Here the earliest stages of the dis ease can be studied a procedure undoubtedly superior to examination of autopsy material —Ed]

Changes in Lymphocyte Count during Acute Pancreatic Necrosis were observed by Karel F Herfort[6] (Charles Univ Prague) Although leukocytosis increased blood sugar con centration increased concentration of amylase in serum and urine and decreased concentration of calcium in the serum are important in diagnosis of acute pancreatic necrosis they are not regular findings Lymphopenia however was observed in all of 38 cases of acute pancreatic necrosis it was not noted in any other acute abdominal disorder Lymphopenia was therefore a reliable diagnostic aid and facilitated conclusions on prognosis and probable extent of the lesion The greater the lymphopenia at onset the more probable was extensive necrosis and poor progno is In less severe cases reduction in the lymphocyte count was smaller

All patients were seen within 48 hours of onset of illness and none had a lymphocyte count above 12 per cent *Low lym phocyte counts in conjunction with the other usual laboratory findings in acute pancreatic necrosis usually indicated a more extensive necrosis and a serious prognosis When lymphopenia disappeared slowly the process was severe but if lymphopenia*

(6) Acta med Sc nd 137 97 103 1950

was quickly replaced by lymphocytosis pancreatic necrosis was probably not pronounced

Chronic Pancreatitis and Lithiasis Pathology and Pathogenesis of Pancreatic Lithiasis are discussed by Hugh A Edmondson Weldon K Bullock and John W Mehl[7] (Univ of Southern California) In 36 000 consecutive autopsies 26 cases were found It is significant that 10 cases were detected in the last 3 000 autopsies when a more careful search was conducted Fourteen of the 26 patients had a history of alcoholism and 8 of diabetes

Deposition of calcium salts was noted only in the outflow tract of the pancreatic juice Calculi were distributed according to two patterns either the main ducts were involved or only the small ducts and acini Microscopic abnormalities were similar to those of chronic pancreatitis but fibrosis dilatation of ducts and parenchymal atrophy were more outstanding

A chemical theory for the pathogenesis is advanced Under normal conditions the pancreatic juice is supersaturated with $CaCO_3$ for the ion concentration will reach values of at least 1×10^{-6} whereas the solubility product is about 5×10^{-8} Thus the precipitation of $CaCO_3$ to form calculi can be explained It has been determined that the principal component of pancreatic calculi is $CaCO_3$ Extreme pancreatic calcification is probably due to deposition of calcium salts in necrotic acinar epithelium

In addition to supersaturation of the pancreatic juice with $CaCO_3$ other factors affecting the ducts in the pathogenesis of calculi include stasis inflammation and accumulation of protein debris

Clinically pancreatic stones should be suspected in patients with diabetes mellitus chronic alcoholism and cirrhosis repeated attacks of upper abdominal pain (especially if pancreatitis is suspected) steatorrhea or unexplained weight loss Small calculi may be formed in the ducts more often than is realized but probably pass into the duodenum

Tests of Pancreatic Function Abbas M Hosny[8] (Univ of Basel) tested the reaction of the pancreas to various substances in 107 middle aged patients with normal gastrointestinal tracts

Technic—A tube was introduced into th duodenum under

(7) Am J P th 26 37 55 J y 1950
(8) C t e t l gia 74 321 339 1948 49

x ray control and three fasting specimens were withdrawn 20 minutes apart The substance to be tested was then given and the contents of the stomach aspirated every 10 20 minutes eight or more times The fluid obtained was stored in flasks chilled and mixed with equal parts of glycerin to preserve enzyme activity

Twelve patients given secretin intravenously reacted in 10 minutes with increased secretion bicarbonate concentration and enzyme output Thereafter the amount of ferment and concentration decreased rapidly while pancreatic secretion and bicarbonate concentration continued to rise A second injection 80 minutes after the first caused immediate rise in secretion and bicarbonate concentration but no change in ferment Secretin plus atropine given seven patients had no effect on bicarbonate concentration but total secretion was reduced The enzyme content was slightly higher than in fasting specimens

Injected at a rate of 40 cc in two minutes intraduodenally hydrochloric acid increased secretion and bicarbonate concentration but not to the degree of secretin alone

Casein intraduodenally had little effect on pancreatic function

*In 11 patients the test was done with 20 cc oil intraduo*denally The tube was clamped for five minutes to keep the oil from escaping A relatively significant rise in total ferment and concentration of secretion was noted after 40 60 minutes Total secretion was also increased Oil appears to affect bile secretion for in one patient the bilirubin index rose to 400

Oil intraduodenally and atropine subcutaneously reduced pancreatic *secretion and bile output in eight patients*

Glucose was given 10 times and caused a slight rise in secretion then gradual diminution *of juice and ferments* after the hyperglycemic state was reached

Insulin (25 units) in 11 patients raised secretion and ferment in 40 60 minutes and bicarbonate concentration kept pace with the increase in secretion All patients became hypoglycemic With the addition of atropine insulin decreased pancreatic function and with secretin added the results were the same as with secretin alone Glucose and hydrochloric acid combined produced no reaction beyond normal

The neural influence on function was tested with atropine adrenalin* and pilocarpine Adrenalin* reduced secretion atropine inhibited it and pilocarpine caused a slight rise

Hosny believes the effect of secretin and hydrochloric acid

to be hormonal and of oil hormonal and neural in hypo or hyperglycemia the pancreas is under neural control

Cancer of Biliary Tract and Pancreas Diagnosis from Cytology of Duodenal Aspirations These cancers annually account for at least 10 000 deaths in the United States partly because of clinical failure to recognize the disease in its early stages Recent revival of interest in cytologic diagnosis of cancer suggested to Henry M Lemon and Walter W Byrnes[9] (Boston) that examination of the sediments of duodenal aspiration might prove helpful in detecting neoplasms of the pancreas biliary tract gallbladder and liver Observations were made chiefly on patients with jaundice of obscure cause observed in the hospital during the past two years including both cancer patients and those with inflammatory disease of the liver biliary tract and pancreas Duodenal fluid was obtained by the usual method of intubation without using oily lubrication Specimens of fasting gastric juice and of A B and C bile were collected separately and centrifuged Moist smears of the sediment were stained using Papanicolaou s method

In most specimens from cancer patients groups of neoplastic cells accompanied normal columnar epithelial cells permitting accurate comparison of the two types (Fig 130) Malignant cells closely resembled the type B cells of Casperson The nuclei were variable in size shape and staining properties with a relative increase in the ratio of nucleus to cytoplasm Large nucleoli and wrinkling of the nuclear membrane were noted Cytoplasm was usually strongly basophilic In some cases it displayed characteristic vacuolation in others phagocytosis of adjacent malignant cells Mitotic figures were not generally seen The prevalence of neoplastic and normal cells in every slide was the most reliable guide in cytodiagnosis of cancer

Data were analyzed for 58 patients of whom 20 had cancer of the pancreas liver or biliary tract Of 16 with pathologically proved cancer the disease was suspected or diagnosed in 11 by cytologic study of duodenal aspirations There were no false positive readings and most diagnoses were affirmative rather than questionable The 11 proved cancers included 2 hepatomas 1 adenocarcinoma of the gallbladder

(9) J A M A 141 254 257 Sept 24 1949

and 1 carcinoma of the common bile duct 1 of the ampulla of Vater 3 of the head of the pancreas 1 of the body and tail of the pancreas 1 metastatic to the liver and pancreas and 1 of the stomach metastatic to the pancreas The five missed cases



Fg 130—O e of ma y cl mps of e pl st cells s nded by t ll ol m no mal p thelial lls fo nd i d od l s d m t (p t t w th c c m of h d f p c s p th log cally sep t d a e mbl g h p t ma × 800 (C te y f Lem n H M nd By re W W J A M A 141 254 57 S pt 24 1949)

included one nonmetastatic hepatoma one carcinoma of the body of the pancreas and two metastatic carcinomas of the liver One carcinoma of the head of the pancreas was missed due to technical failure Two additional cases were diagnosed clinically and cytologically as cancer of the biliary tract Al though the patients died within six months with a picture con sistent with the diagnosis pathologic proof was not obtained

In 25 per cent of the control cases a strong clinical impression of cancer was not confirmed either by smears or by the subsequent course of the disease In most of these the smears indicated either calculi or inflammatory disease

Cytologic examination of the sediments of duodenal aspiration seems a valuable indication of cancer primary in the glandular epithelium of the gallbladder extrahepatic bile ducts and pancreas it should become a routine procedure on all duodenal drainages This method provides the most hopeful technic yet described for early detection of these tumors Two additional cases in which pancreatic carcinoma was diagnosed preoperatively by exfoliated cancer cells in duodenal drainage have recently been reported by McNeer and Ewing

Carcinoma of Pancreas Clinical and Pathologic Analysis of 39 Autopsied Cases is presented by W B Leach[1] (McGill Univ) The head of the pancreas alone was involved in 21 cases the body in 9 and the tail in 2 In seven the exact origin of the carcinoma could not be determined The direction and effect of local extension in carcinoma of the pancreas depend on the location of the tumor and its relation to adjacent structures The common bile duct was involved in 16 cases of cancer of the head of the pancreas but in only two cases in which the tumor was in the body or tail alone

The usual gross and microscopic pathologic changes of carcinoma of the pancreas were observed Carcinoma of the body or tail metastasizes more often and more extensively than carcinoma of the head Secondary invasion of the lungs occurred in 13 cases 4 of which originated in the head of the pancreas In three instances an erroneous diagnosis of bronchogenic carcinoma was made It was supported in one case by a positive bronchoscopic biopsy but pathologic examination in all disclosed that the lung tumors were metastases Venous thrombosis was not prominent but occurred about as frequently as would be expected with other abdominal cancers

The commonest initial complaint in 30 patients was weakness and weight loss In 28 there was abdominal pain which appeared to be of greater symptomatic importance than weight loss Average duration of pain before death was seven months in cases of longer duration pain was usually inter

(1) Am J P th 26 333 347 M h 1950

mittent There was jaundice in 15 cases clay colored stools in 12 and dark urine in 8 Average duration of each was 39 7 and 5 weeks respectively This triad is more commonly associated with cancer of the head of the pancreas than with that of the body or tail Constipation was more common than diarrhea and nausea and vomiting occurred in a third of the cases A palpable abdominal mass was present in about 50 per cent on admission definite enlargement of the liver was noted in 23 The relatively late onset of symptoms of sufficient severity to cause a patient to consult a physician and the inconstancy of signs and symptoms account for the low accuracy of clinical diagnosis and the difficulty of accurate preoperative localization of a pancreatic tumor

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INTESTINAL TRACT

Study of Action of Prostigmin® on Bowel of Human Beings was made by John M McMahon (Mayo Found) Charles F Code William G Sauer and J Arnold Bargen[2] (Mayo Clinic) A tandem balloon recording system was placed in the bowel of each of 12 fasting patients with enteric stomas two of the ileum five of the transverse colon and five of the sigmoid colon Depending on the type of stoma the balloons were inserted in either an orad (antiperistaltic) or caudad (properistaltic) direction until well beneath the abdominal wall Twenty to 30 cc water was injected into each balloon After a control period of 2½ 3 hours on the first morning and an additional 30 minutes on the second morning 0 5 mg prostigmin® methylsulfate was given intramuscularly Recording was continued for two or more hours

Records of five patients were examined in detail Division of intestinal motility into propulsive and nonpropulsive phases using the three typical waves originally defined by Templeton and Lawson was followed (Fig 131) A definite change in the character of bowel activity occurred two to *eight minutes after prostigmin® injection* Type I and III waves decreased in number The number of type II waves in

( ) Ga t oenterology 1 970 977 Ju e 1949

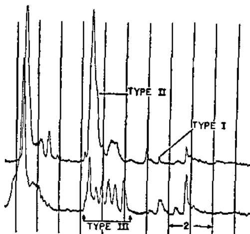


Fig 131 —Typ f .o t ct n h m n c l N drug w dm t d Upp t g w m d f m d d gm t low t g f m ph l d segment. Typ l typ I II d III t to m k d D tan betw t l l p t m t (Cou t y f M M b n J M t l G t o- t l gy 1 970 977 J e 1949)

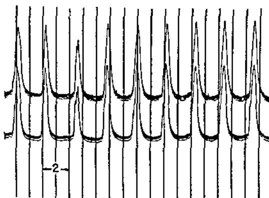


Fig 13 — P t gmi ⊗ bythm Uppe t g w m d f m d d b l loo l w t ci g f m ph l d b ll Not i n t f typ II w be tw dia t gment u g t g l t ls D ta b tw n t l m k p ent m t (C te y of M M hon J M t l G st nt l gy 12 970 977 J 1949)

creased with a corresponding increase in their strength and in incidence of co ordinated contractions The increase in pro pulsive motility was characterized clinically by expulsion of gas and feces All patients had moderate to severe abdominal

cramps In six patients prostigmin® rhythm' developed 6-74 minutes after injection and persisted for an average of 68 minutes Records from both segments of the bowel showed only co ordinated type II waves occurring usually at one to two minute intervals (Fig 132)

When compared with the control period prostigmin® injection produced a change in bowel motility rather than the initiation of or increase in total activity Propulsive activity of the bowel was increased and mixing activity decreased This observation suggests a co ordinating action of prostigmin® on the intestine, probably through the conducting system of the bowel

Effect of Vomiting Due to Intestinal Obstruction on Serum Potassium Chemical and Electrocardiographic Observations in 15 Cases, Preliminary Report. Samuel Bellet Carl S Nadler Peter C Gazes and Mary Lanning[3] (Philadelphia) emphasize the value of the electrocardiogram in diagnosis of hypopotassemia Among the authors 15 patients hypopotassemia resulted from loss of potassium and gastric content vomited because of duodenal ulcer carcinoma of the bowel or stomach strangulated hernia or cholelithiasis with peritonitis and obstruction Some patients were so severely dehydrated that they had mental symptoms and many presented the picture of shock

Serum potassium values were 2 3 2 5 m Eq /L in 4 patients and 2 5 4 1 m Eq in 11 In general serum potassium values varied with degree of alkalosis

S T segments were depressed T waves flat or inverted and Q T segments prolonged Extrasystoles were detected in five patients Electrocardiographic abnormalities were rectified by administration of potassium but not altered by administration of calcium

Potassium deficiency is associated with familial periodic paralysis diabetic acidosis chronic nephritis and vomiting and should be suspected if muscular weakness atony or paralysis is present Administration of glucose accentuates hypopotassemia

Darrow estimated that 3 5 mM potassium or 0 26 Gm potassium chloride/kg is a safe dose if given during four hours or more preferably by hypodermoclysis

(3) Am J M d 6 712 724 J n 1949

Effects of Uronic Acids, Pectins and Pectinates on Enteric Flora, Alone and in Combination with Antibiotics In Vitro Studies are reported by Wilfred E Wooldridge and George W Mast[4] (Washington Univ) It was found that unbuffered solutions of 7 per cent and of 5 per cent methoxyl pectinic acid bismuth pectinate aluminum pectinate silver pectinate galacturonic acid hydrate or glucuronolactone possess anti bacterial properties against Staphylococcus aureus Pseudo monas aeruginosa and Escherichia coli Such properties were not dependent on pH since bactericidal action took place in pH ranges well above that lethal to the organisms Pectinic acids were least potent pectinates with the exception of the silver salt were intermediate silver pectinate and galac turonic and glucuronic acids were most effective Pectins with the highest methoxyl content were consistently the most bac tericidal

Combining streptomycin with test compounds in vitro produced mild synergism even though the substances were all well below their bactericidal concentrations This syner gism did not approach that which functions clinically The same degree of synergism occurred with penicillin bacitracin or tyrothricin There was no change in the effective spectrum of these antibiotics due to their combination with test com pounds Organisms resistant to a certain antibiotic showed no change in resistance due to various combinations Ps aeru ginosa was the organism most affected by these compounds

A technic by which any part or all of the gastrointestinal tract can be sterilized offers numerous possibilities for further study Study of the physiologic effect on the host of more satisfactory preparation for gastrointestinal surgery and of conditions in which enteric autointoxication is thought to be an etiologic factor are only a few of these

Transformation of Widal's Digestive Hemoclasis into Postprandial Physiologic Leukocytosis by Converting In testinal Dysmicrobism State into Eumicrobism State Charles Amerling[5] (Olomouc Czechoslovakia) explains what R Goiffon has termed intestinal eumicrobism i e a state of microbism of the colon in which the level of organic acids and amino acids is below normal (below 15 for the former

(4) Am J Surg 78 881 886 December 1949
(5) Presse méd 57 1158-1159 Dec 17 1949

and below 4 for the latter) He points out that the allergic shock observed in the state of intestinal dysmicrobism may commonly turn into physiologic postprandial leukocytosis when the state of eumicrobism has been established By this *method he has been able to control attacks of asthma in 80* per cent of his asthmatic patients and to obtain more satisfactory desensitizing results than with any other method

To change the intestinal dysmicrobism to eumicrobism Amerling imposed a severe diet consisting of potato soup always prepared in the same manner and consumed in definite amounts 10 dg potato 1 dg butter, 2 dg flour, ¼ L water In a case cited as an example the patient passed to the state of intestinal eumicrobism six days after the beginning of the diet reaction of the feces was alkaline value of organic acids was 12 and that of amino acids 3 2 attacks of asthma were slight decrease in leukocytes was less than at the beginning of the experiment Five days later reaction of the feces was still alkaline value of the organic acids 10 and that of the amino acids 2 but the hemoclastic crisis did not occur (first phase of allergic shock) Instead there was a physiologic post prandial leukocytosis The organism did not react to the allergen diet by a hemoclastic crisis and by the same token the second phase of the anaphylactic shock i e the attack of asthma could not occur

Thephorin* (Phenindamine) in Treatment of Gastrointestinal Allergy Eugene M Schloss[6] (Philadelphia) studied intralumenal jejunal pressure in intestinal allergy and established that certain foodstuffs presumably allergenic caused changes in intrajejunal pressure and its rhythmic fluctuations These changes occurred independently of the simple distensive effect of water inclusion of sodium chloride or glucose, and chemical or hormonal activities involved in the introduction of a foodstuff per se In investigating the possibility of modification by antihistaminics Schloss studied the efficacy of thephorin* in 41 patients with digestive complaints

Intubation studies were made on eight patients given 25 mg thephorin* orally one half hour before introduction of a known food allergen Amplitude and rhythm of phasic pressure waves were not appreciably altered by the food An additional 33 patients with proved gastrointestinal food allergies

(6) Gastroenterology 13 311 318 October 1949

were given 25 mg thephorin® three to four times daily when the drug was administered after 7 p m ½ gr phenobarbital or 100 200 mg presidon® was added Diet included specifically allergenic foods in small quantities at least twice daily When the patient remained symptom free quantities were increased to normal daily amounts At irregular intervals thephorin® was withdrawn Tablets of similar appearance were substituted or all medication was suspended Continued ingestion of allergenic foods was followed by reappearance of symptoms within 24 72 hours Such recurrence was similar in type and severity to that suffered before therapy

Thephorin® completely relieved 69 and partially relieved 26 of the 126 individual symptoms a total of 75 per cent symptom amelioration Of the 41 patients 26 (63 per cent) obtained complete relief As expected relief was greatest from symptoms due to abnormal intestinal tonus or aberration of motility Eighteen of 23 patients with diarrhea obtained complete relief and 2 others partial relief Of 11 patients with nausea 7 reported complete relief and 2 others definite improvement Of 16 having abdominal pain within one-half hour after meals 44 per cent had complete relief and 25 per cent a decrease in pain of 12 with fulness within one half hour after eating 50 per cent were completely and 17 per cent partially relieved Maximal benefit was reported by those with pain and fulness one half to two hours after food Vomiting substernal distress heartburn and belching were not affected by thephorin® in the dosages used

Although such therapy is not curative thephorin® is valuable in symptom control during specific desensitization in palliation of symptoms when desensitization is impracticable and in the crude delineation of gastrointestinal allergy in patients without evidence of organic digestive disease when differentiation from functional and neuropsychiatric factors is indicated Possibly the combination of antihistaminic and anticholinergic effects of thephorin® as evidenced in animal studies was responsible for the symptom relief observed

Observations on Small Intestinal Hypomotility and States of Hypertonicity Arising from Functional Bases, as determined by x ray studies of the small intestine after a barium meal are reported by Lay Martin[7] (Johns Hopkins Univ)

(7) Am J M d 8 196 204 F bru ry 1950

Physical examination of 11 women and 16 men, aged 26 61 showed no evidence of acute or chronic disease which might influence motility or tone Laboratory studies were not indicative of important abnormalities Abdominal examination did not suggest intraperitoneal disease or partial obstruction to intestinal motility Barium left the stomachs in less than five hours

In all ileostasis was detected by x ray in the absence of organic disease Some patients were chronically fatigued both physically and mentally and intestinal motility returned to normal after a period of rest In others hypomotility was associated with an abnormally low metabolic rate and abnormally high concentration of serum cholesterol When these patients were given thyroid extract hypomotility disappeared In patients with anxiety or tension states hypertonicity of the small intestine and spasm of the ileocecal junction may have been present None of the patients showed evidence of vitamin deficiency These observations indicate the importance of differentiating organic and functional causes of ileostasis

Hysterical Type of Nongaseous Abdominal Bloating Walter C Alvarez[8] (Mayo Clinic) describes a syndrome consisting of pronounced bloating due to contraction of abdominal muscles and often to assumption of a lordotic posture which forces the abdomen forward Commonly the swelling increases gradually during the afternoon and decreases at night without passage of gas X rays of a bloated abdomen never show excess of gas and exploratory operations reveal no physical cause

In a series of 92 patients 85 of whom were women and 7 men almost all were nervous unhappy neurotic or psychopathic Many were relatives of insane persons or of persons with epilepsy migraine or diabetes Most patients had good digestion between and sometimes during attacks of bloating

Bloating often began after excitement annoyance fright or fatigue Physical and laboratory examinations failed to show a contributory cause The abdomen became flat a few seconds or minutes after (1) induction of spinal or general anesthesia (2) blocking of splanchnic nerves with procaine (3) onset of vomiting (4) administration of morphine, (5) doubling up so as to alleviate lordosis Most patients lost the

(8) Arch Int. Med 84 217 245 August 1949

bloated appearance when lying down especially if thighs were flexed on the abdomen The nervous storm which seemed to produce contraction of the abdominal muscles appeared to quiet the bowel in some cases the attack ended after a gurgle was heard in the abdomen

No effective safe way was found to terminate attacks Prognosis for recovery is poor but some patients recover when life becomes easier or happier Exploratory operations should not be performed If surgery is proposed during an acute attack and swelling goes down during anesthetization a diagnosis of functional bloating should be made and operation discontinued

[A marked descent of the diaphragm during the seizure wa observed recently by one investigator To this mechanism he largely ascribed this bizarre phenomenon —Ed]

Diagnosis and Treatment of Celiac Disease Report of 603 Cases Sidney V Haas and Merrill P Haas[9] (New York City) consider celiac disease to be an altered intestinal function characterized by appearance of abnormal stools which are more frequent than usual and altered in physical characteristics The most important and characteristic symptom is diarrhea which may exist from birth or begin any time thereafter The stool is usually soft and mushy more voluminous than in health and pale cream to greenish yellow A common symptom is irritability and obvious unhappiness Next in frequency is failure to gain weight and to grow There is some evidence of a familial tendency toward the disease

All pathologic abnormalities found in celiac disease are encountered also in other conditions Though the stool contains excess fat and blood sugar curves are usually low no laboratory procedures reveal conditions which make definite diagnosis possible Diagnosis must depend on clinical symptoms history and the effect of the strict celiac diet

The specific carbohydrate diet which cures celiac disease initially is comprised of bananas and protein milk

Diet Preparation —Protein milk is prepared by warming 1 qt milk to 98 F adding 1 tablespoon of essence of pepsin and draining the mixture through cheesecloth for a half hour to separate the whey from the curd The curd is mixed with 1 pt water and rubbed through a fine wire strainer several times before 1 pt buttermilk is added The whey which contains the sugar is discarded

Calcium caseinate milk may be served instead of protein milk

(9) P tg d Med 7 239 250 Ap 1 1950

It is prepared by adding 4 6 tablespoons of calcium caseinate (casec®) to 1 pt water and 1 pt milk after the casec® has been mixed with enough cold water to form a paste The whole mixture is brought to a boil while stirring constantly boiled actively for one minute removed from the fire and allowed to cool If necessary to sweeten one or two tablets of saccharin (1 gr) may be added

If ripe bananas are not available or their use practical banana powder may be substituted as the exact equivalent Dried banana flakes do not always give as satisfactory results as fresh ripe bananas

The basic diet at the beginning of treatment consists of pot cheese bananas and protein milk for breakfast Lunch and supper are the same and comprise meat pot cheese bananas protein milk and gelatin Any of these foods may be used in any quantity or given between meals After one week orange juice other cheeses and egg may be added one at a time with a sufficient interval to test the acceptability of each After two weeks all fresh fruits may be tried in the same way When stools are controlled vegetables except potato may be added Sometimes these are well tolerated but often their introduction must be postponed Tolerance is eventually attained at which time the diet is complete Vitamin B complex with folic acid and aqueous soluble preparations of vitamin A and D should be taken The diet must be continued at least one year

Most patients begin to improve immediately the earliest sign being a change for the better in the child s disposition Diarrhea is often controlled in the first week but in some cases may take months During the first six months or more any infection especially in the upper respiratory tract may be accompanied by recurrent diarrhea Also in this period ingestion of a forbidden carbohydrate brings about loose stools within hours or days but the attack quickly subsides if no more carbohydrates are ingested The strict celiac diet must be continued at least 1 year and as a rule the entire cure requires no more than 18 months When cure is obtained there should be no relapse Acceptance of a slight diarrhea for four or five years until the child outgrows it is fallacious and harmful to the patient Pulmonary involvement is unusual and rarely fatal with the proper therapy No avitaminosis was observed in any of these patients

Of 370 patients adequately followed 270 were cured 89 are still being treated but responding favorably 8 were not cured and 3 died Cure is considered tolerance for a full normal diet at the end of three years

It is postulated that forbidden carbohydrates cause diarrhea by acting as a laxative substance They are probably con

verted in the gut lumen to a substance which is irritating to smooth muscle Tolerance for these polysaccharides after adequate treatment may occur because of a readjustment of the enzyme system to proper splitting of carbohydrates or result from disappearance of bacteria from the intestine

Symptomatic Sprue Study of Six Verified Cases was made by Chr Juel Bjerkelund[1] (Univ Hosp Oslo) Primary causes for the sprue syndrome were reticulosarcoma in one lymphogranulomatosis in small intestine and mesentery in two cystic lymphangiomas of the mesentery in one and severe enteritis with lymphadenitis in two patients

Five patients died The sixth who had severe nonspecific regional jejunitis recovered after about a year s illness possibly as the result of x ray treatment In one case autopsy disclosed many enlarged cystic lymphangiomas in the mesentery filled with inspissated chyle Though symptoms of adrenal insufficiency have been frequently reported in association with idiopathic steatorrhea no patient showed signs of adrenal insufficiency but in two both adrenals were diffusely infiltrated by tumor cells

The primary pathologic changes in symptomatic sprue are found in the lymphatics of the mesentery The mucosa of the intestine is affected either primarily or secondarily as a result of disturbed circulation in the mesentery Reduced fat absorption alone cannot explain development of the other symptoms of sprue Steatorrhea may be explained by the mechanical blockage of lymphatics in the intestine and mesentery but that this alone is the cause of reduced fat absorption is doubtful Complicated chemical processes such as phosphorylation which are important for absorption of fat and other nutritive elements may be altered and therefore are of etiologic significance The low oral sugar tolerance curve may be caused by reduced absorption of sugar from the intestine Reduced fat absorption may facilitate protein deficit and hypoproteinemia Hypocalcemia may result from hypoproteinemia increased loss of calcium through feces by formation of insoluble calcium soap in the intestine or reduced calcium absorption because of vitamin D deficiency Anemia and vitamin deficiency symptoms may result from deficient absorption of dietary essentials Hypoprothrombinemia may be partially a result of

(1) Acta med. Scand nav 137 130 149 1950

altered bacterial flora in the intestine since it does not always correspond to the degree of steatorrhea

Evaluation of Influence of World War II on Incidence of Amebiasis David R Lincicome Walter H Thiede and Eliza beth Carpenter[3] (Univ of Wisconsin) performed single stool examinations on 1 110 students of whom 57 3 per cent had military service overseas 25 6 per cent had domestic service only and 16 5 per cent were not in the armed forces Incidence of Endameba histolytica in these groups was 4 5 2 5 and 1 6 per cent respectively The average percentage positive for the whole group was 3 5 per cent

In comparison the incidence of E histolytica in 11 236 nonservice college students examined between the two wars was 4 9 per cent On this basis the incidence of E histolytica in student populations is probably not greater than it was be fore the war A reported incidence of 14 7 per cent among 50 517 World War II military personnel with domestic and overseas service does not reflect any circumstance in military life favoring infection because it is comparable to the ex pected rate in the general population in this country How ever when compared with similar groups three years after the war this rate seems to be significantly higher There has probably been little change in the incidence of amebiasis as a result of the war

Preliminary Report of Successful Treatment of Amebiasis with Aureomycin Observation of the effect of aureomycin hydrochloride on the gross character and bacterial flora of fecal matter led L V McVay R L Laird and D H Sprunt[4] (Univ of Tennessee) to investigate its use in treatment of amebiasis One of three cases studied is presented here

Negro aged 63 complained of paraumbilical pain abdominal ful ness and constipation Both trophozoite and cystic forms of Endameba histolytica were found in the stool Stools became nega tive following oral administration of 6 75 Gm aureomycin in divided doses over three days The patient received a total of 21.75 Gm aureomycin All gastrointestinal symptoms disappeared and over a three week period 14 stool examinations were negative for ameba

In vitro activity of aureomycin was studied on strains of E histolytica isolated from the three cases Aureomycin in amounts varying from 0 2 to 3 2 mg /cc of overlay was intro

(3) Am. J Trop M 1 30 171 179 M r h 1950
(4) Sc ence 109 590-591 J 10 1949

duced into heavily positive cultures At the end of 48 hours no amebas were found in cultures containing aureomycin whereas control cultures remained strongly positive

Eleven additional cases were successfully treated with no recurrence of symptoms

[Another faculty associate of the authors John D Hughes reported results of treatment with aureomycin in 38 rather refractory cases (J A M A 142 1052 1054 Apr 8 1950) Each patient received 28 capsules of aureomycin (0.25 Gm) over a period of four to seven days 71 per cent were "cured" The nausea so commonly induced by the antibiotic, was controlled by antacids belladonna and barbiturates and the abdominal cramps by paregoric. Rectal and perianal burning was a frequent side effect Although the use of aureomycin is so recent that optimal dosage schedules have not been established Hughes advised larger doses being taken over a longer period —Ed]

Postdysenteric Colitis G T Stewart[5] (Liverpool) reports that of 627 cases of dysenteric disorders seen in Ceylon 50 per cent were classified as intestinal amebiasis and 37 per cent as bacillary dysentery The incidence of recurrences and relapses of diarrhea among patients with these conditions is shown in the table The relapse rate among patients with ba

RELAPSES AND RECURRENCES OF DIARRHEA IN AMEBIASIS AND BACILLARY DYSENTERY

G p	T No	Recu ences ter Tre m			
		W th n 3 Wk		W th 3 M	
		O g n m	D b †	O g m	Dia heat
Bacillary dysentery (123)					
S shigae	12	1 (1 death)	1	—	4 return cases with E. histolytica
S schmitzii	6	—		–	
S flexneri	30	—			
S sonnei	26	16	6	6	
Others	10	—		–	
Diagnosed by exudate	39	—	1	—	
Intestinal amebiasis (100)					
Dysentery	54	2	10	4	17
Chronic diarrhea	46		8	2	12
Dual infection	5	–		2	2

Incl d g cases w th l pse fte f th cou se f t tme t.
†W th or w thout o g sm

cillary dysentery adequately treated with sulfonamides was negligible In contrast there were many recurrences among patients treated for active intestinal amebiasis Not all recurrences were accounted for by persistence of Endameba histolytica

These findings were substantiated by analysis of 246 cases

5 rit. M J 1 405 409 F b 18 1950

of acute and chronic diarrhea in navy personnel returning from the tropics and admitted to the Tropical Diseases Center at Liverpool Bacillary dysentery accounted for 2 intestinal amebiasis for 174 and other infections for 21 In addition there was a group not definitely represented among the cases seen in Ceylon—49 cases of postdysenteric colitis in which diarrhea persisted in the absence of any recognizable intestinal pathogen

The main complaint in these cases of postdysenteric colitis was diarrhea but there were signs of lassitude weight loss and abdominal pain Sigmoidoscopic and stool examinations showed that the patients could be divided into two main types In one type (55 per cent) the colon mucosa was normal and the stools contained no exudate or a scanty mucoid exudate In these cases slow natural improvement occurred without treatment In the second but more important type (45 per cent) there were inflammatory or ulcerative changes in the colon with blood and pus in the feces Most of the patients with postdysenteric colitis had had amebic dysentery the others had had bacillary dysentery or a dual infection

The fact that some patients in the second group showed improvement on antibacterial treatment indicates that a non specific type of bacterial infection may be the causative agent On the other hand other patients showed no response to anti bacterial treatment suggesting that the lesion is similar to that of idiopathic ulcerative colitis

Ileojejunitis Burrill B Crohn[6] (New York City) reports 38 cases of ileojejunitis an inflammatory granulomatous dis ease of the small bowel closely allied to regional or terminal ileitis Specific causative agents are unknown In contrast to regional ileitis the disease affects youth predominantly men with greatest incidence in the second and third decades There were 27 men and 11 women a ratio of almost 3 1 in this series

The lesions were grouped according to anatomic and patho logic variations (1) Progressive jejunal involvement by up ward extension from an old regional ileitis may occur spon taneously early or late in the disease or in the form of recur rences following surgical resection or short circuiting proce dures (2) Diffuse involvement either by continuity or in a

(6) New Y k Stat J Med. 49 1808 1811 Aug 1 1949

discontinuous manner with lesions interspersed with normal mucosa is the commonest form comprising 24 of the 38 cases In two cases the duodenum was involved (3) Lesions involving isolated areas of the jejunum usually near the fossa of Treitz occurred in nine patients (4) The combination of isolated lesions in both the jejunum and the distal ileum independent of each other and without evidence of extension was found in three patients

The disease is characterized by low grade fever mild diarrhea in most cases severe abdominal pain weight loss anemia malnutrition and vitamin deficiencies Fistulas and gross hemorrhage and obstruction are rare Since the disease usually starts before puberty secondary sexual growth is usually delayed Hypoproteinemia pedal edema splenomegaly and clubbing of fingers may follow the severe metabolic disturbances Hypocalcemia may initiate symptoms of tetany Roentgenograms show sacculations and constrictions of the small intestine with scattered collections of barium from loss of normal mucosal folds and markings The picture is somewhat that of sprue however in sprue the changes are reversible with vitamin therapy in ileojejunitis they are irreversible The appearance of polyps confirms diagnosis of ileojejunitis for polyps do not occur in sprue

Progno is depends on degree and type of involvement Recovery may be spontaneous or may follow surgery on the other hand chronic invalidism may result In this series of 13 patients who improved 5 had resections of localized lesions In six patients the end result was only fair seven did not improve and six died In six patients there was no follow up

Medical treatment attempts to overcome the infection and to restore nutrition and weight No present antibiotic or chemotherapeutic drug has specific action on the disease At times use of sulfasuxidine* sulfathalidine* or sulfacetamide seems to close draining fistulas Symptomatic therapy includes transfusions infusions high protein diet including protein hydrolysates and injections of crude liver extract and vitamin B complex

Surgery is limited to localized lesions When the disease is an extension upward from ileitis and when diffuse ileojejunitis exists surgery will be of no avail Fortunately in the diffuse type recession of lesions is common Surgery is most

successful in isolated high jejunal lesions Short circuiting alone usually fails and often resection is then required In isolated ileal and jejunal lesions simultaneous resection of the jejunal lesion and short circuiting of the ileal give excellent results

[The profession is greatly indebted to Crohn for his original and illuminating investigation of gastrointestinal tract diseases particularly inflammatory granulomatous lesions of the small intestine In my article introducing this section I called attention to such lesions involving even the stomach and upper duodenum In lesions confined to the small bowel itself Maingot prefers the term regional enteritis since it probably indicates the most important feature of the condition—its nonspecificity—and emphasizes the fact that the lesion is inflammatory and not neoplastic —Ed]

Diverticula of Colon Report of 274 Cases is made by Eugene J Morhous[7] (Clifton Springs Sanitarium and Clinic) This group represents 0 56 per cent of 48 609 hospital admissions over 15 years Distribution between sexes was almost equal Diverticula were associated with carcinoma of the colon in three and with carcinoma of the sigmoid in two cases Review of 145 cases of carcinoma of the colon showed an incidence of diverticula of 3 4 per cent

Constipation flatulence lower abdominal pain and tenderness with or without a palpable mass were the most commonly encountered signs and symptoms X ray examination of the colon with a barium enema was the most valuable diagnostic aid establishing the diagnosis in 82 8 per cent of cases The characteristic sign consisted of rounded knoblike extensions from the lumen of the colon Diverticula occurred predominately in the sigmoid area Proctoscopic examination was of little value diagnosis being made by this method in only 3 of 59 cases

Treatment is directed mainly to prevention of infection A low residue bland diet with avoidance of fruits containing fine seeds is recommended Regular bowel habits without use of laxatives is the ideal aim but is difficult to achieve Obesity should be corrected and general health promoted Excessive use of condiments should be avoided and the patients should drink two glasses of water at each meal Harsh irritative cathartics are contraindicated Cool tap water enemas once or twice a week may aid in elimination if mild laxatives are ineffectual

(7) New York State J Med 50 689 692 Ma 15 1950

If diverticulitis is present treatment is essentially the same except that bed rest is imperative until signs of infection have subsided Heat to the abdomen may help relieve pain and adequate doses of belladonna or atropine may relieve bowel spasm Enemas may prove dangerous if not given carefully and should be limited to small quantities of warm olive oil or cottonseed oil daily Surgery should be reserved for complications such as peritonitis following perforation unresolved abscess obstruction and fistula and for cases in which differentiation between carcinoma and diverticulitis cannot otherwise be made

[The prevalence of this disorder makes it a subject of perennial interest Last year a review of 726 consecutive cases was presented by Goodwin and Collins (1949 YEAR BOOK OF MEDICINE p 790)

Of added interest is a review of 389 patients with diverticulitis treated surgically by Pemberton Black and Maino (Surg Gynec & Obst 85 523 534 October 1947) They found that establishment of a colonic stoma orad to the lesion was followed by excellent results as long as the stoma was maintained However only a third remained well when closure of the stoma was not followed by resection Resection was favored in all cases of diverticulitis in the absence of proof of complete subsidence of the inflammatory process Operative risk has been greatly reduced by chemotherapy —Ed]

Generalized Intestinal Polyposis and Melanin Spots of Oral Mucosa Lips and Digits Syndrome of Diagnostic Significance *Harold Jeghers (Georgetown Univ) Victor A McKusick* (Johns Hopkins Univ) and Kermit H Katz[8] (Boston Univ) report 10 cases of this syndrome All patients were of dark complexion and seven were females

In each case in which data were available it was found that pigmentation had been present from early in childhood to age 20 or more with little or no change over the years and no tendency to fade before that time Pigmentation was most striking on the lips (Fig 133) and buccal mucosa (Fig 134) It occurred as round oval or irregular patches of brown or occasionally almost black pigment The histologic appearance of a typical pigmented spot is shown in Figure 135 Study of this section revealed that pigment particles in the epidermis occur mainly in vertical bands Clinically some of the spots had a somewhat stippled appearance under magnification which could be explained by the curious histologic pattern None of the patients had melanosis coli as evidenced by sigmoidoscopy or inspection of colonic mucosa in operative

(8) N w E gl d J M d 241 993 1005 D 2 1031 1036 D 29 1949

Fig 133 —App ne of o f thors pat nt Ch r t r t c d loc l a t on of spot on l p m *e m* k d on ow l p s w ll demo t t d Not rel t p t of pots l wh on fa e (Cou te of J gh s H *t al* New E gl nd J Med 241 993 1005 Dec 2 1949)

Fig 134 —Same c se a p ec d g howi g m lan l d of mouth. (Co t y f Jegh r H *t l* N w E gla d J M d 241 993 1005 1949)

or autopsy specimens When carefully looked for pigmented areas could be seen on the fingers of each patient and in some on the toes also None of the pigmented spots were elevated vascular or hairy The pigment of this syndrome is undoubtedly melanin

The other portion of the syndrome consists of intestinal polyposis Polyps may be distributed throughout the entire intestinal tract but their most striking clinical manifestations are referable to the small intestine with numerous episodes



Fig 135—S m H t l gı ppea f m l pot b p y p m
f skin (C t y f J gh H el l N w E gl nd J M d 241 1031 1036 D
29 1949)

of abdominal pain and signs of minor obstructions terminating in one or more attacks of small bowel intussusception Surgery was performed on these 10 patients from one to four times for such symptoms By contrast rectal and large bowel symptoms and signs were minimal or absent Operation or autopsy revealed most of the polyps to be in the small intestine in all cases Polyps were also found in the stomach and colon in the three cases in which autopsy was done Most of the polyps were adenomatous but in one case they had become malignant No report has been found with adequate bowel study in which the pigmentation portion of the syndrome was associated solely with large bowel polyposis

In this series two families are represented by three cases each The syndrome appears to be inherited as a simple mendelian dominant The characteristics constituting the syndrome

appear to have a high degree of penetrance and probably oc cur in most of those with the necessary factors There are no generation skips Both males and females carry the factor and both are affected about equally The full syndrome poly posis and spots has always occurred in the same person There must therefore be a single pleiotropic gene responsible for both characteristics

Studies in Ulcerative Colitis Study of Personality in Relation to Ulcerative Colitis, based on observation of 20 pa tients is reported by V P Mahoney H L Bockus Margaret Ingram J W Hundley and J C Yaskin[9] (Univ of Pennsyl vania) All cases were examples of chronic ulcerative colitis of the ordinary type in which at least the rectum sigmoid and descending colon were involved In 11 instances the entire colon was involved

Every patient had definite neurotic traits such as tension inability to assert self anxiety and sensitivity as revealed by the psychiatric interview method Also present were hostility and immaturity in 19 guile and indecision in 18 passivity in 15 dependency and conscientiousness in 15 aggression and perfectionism in 12 and estheticism in 6 The Rorschach test was performed in all but 1 patient and revealed inability to respond to stimulation in the environment in 19 immaturity and anxiety in 18 guilt lack of flexibility in thinking and lack of ambition in 17 indecision and hostility in 13 exces sive phantasy life in 11 aggression and passivity in 9 perfec tionism in 12 and psychotic trends in 1 Study of the early developmental factors showed considerable emotional illness in the family major disturbances in the parent child and sib ling relationships and many early traumatic experiences not specifically related to the intestinal tract

These studies do not disclose the reason for localization of the pathophysiologic process in the colon Obviously none of these personality traits when taken alone is specific for ulcerative colitis The understanding of such traits may be useful in treatment of these patients

Significance of Hyperalimentation in Treatment of Chronic Idiopathic Ulcerative Colitis Thomas E Machella[1] (Hosp of Univ of Pennsylvania) compares results obtained in treat

(9) Gastroenterology 13 547 563 December 1949
(1) Am J Med 7 191 197 August 1949

ment of 13 patients by oral administration of a hydrolysate and dextri maltose* solution with those for 12 patients pre viously treated with the same diet and medical ileostomy the intubation of the small intestine to place the colon at rest Patients treated without intubation were severely ill with average weight loss of 20 lb stools averaged 6 to 11 1 per 24 hours Hospitalization averaged 32 7 days and strict pro tein hydrolysate therapy 24 4 days Clinical findings for the group managed by medical ileostomy were comparable

PROCEDURE —The diet consisted solely of a mixture of equal parts protolysate* and dextri maltose* no 2 The amount for each day's feeding calculated on the basis of 20 calories/lb of pre illness weight was dissolved in boiling water to yield a 15 25 per cent solution and was stored on ice From 200 to 400 cc. were in gested every two hours from 6 a m. to 10 p m All patients received iron and vitamins plus blood transfusions and psychiatric treatment when indicated. When improvement was observed a high protein high caloric low residue diet was gradually substituted

This treatment induced satisfactory remissions in all 13 patients General improvement was reflected subjectively as well as by objective signs such as subsidence of fever and anorexia increase in body weight decrease in stool frequency and improved sigmoidoscopic and roentgen appearance of the colon One relapse probably due to emotional disturbances was re treated successfully

Results in the 12 patients treated by intubation plus pro tein hydrolysate diet were similar All patients in both series are clinically well Medical ileostomy is now reserved for spe cial cases the hyperalimentation regimen being effective in most uncomplicated cases

Ileostomy and Ulcerative Colitis In the treatment of ul cerative colitis *apart from its complications surgery* has one aim to put the colon at complete rest This can be done only by ileostomy However ileostomy too often becomes the last resort when the patient s condition is critical Since this opera tion is rarely necessary as a lifesaving measure it should always be carefully planned with the patient in the best pos sible mental and physical health T L Hardy B N Brooke and C F Hawkins (Birmingham England) advocate earlier and more frequent performance of terminal double ended ileostomy preceded by careful psychologic preparation of the

( ) Lancet 2 5 9 J ly 2 1949

appear to have a high degree of penetrance and probably occur in most of those with the necessary factors There are no generation skips Both males and females carry the factor and both are affected about equally The full syndrome poly posis and spots has always occurred in the same person There must therefore be a single pleiotropic gene responsible for both characteristics

Studies in Ulcerative Colitis Study of Personality in Relation to Ulcerative Colitis, based on observation of 20 patients is reported by V P Mahoney H L Bockus Margaret Ingram J W Hundley and J C Yaskin[9] (Univ of Pennsylvania) All cases were examples of chronic ulcerative colitis of the ordinary type in which at least the rectum sigmoid and descending colon were involved In 11 instances the entire colon was involved

Every patient had definite neurotic traits such as tension inability to assert self anxiety and sensitivity as revealed by the psychiatric interview method Also present were hostility and immaturity in 19 guile and indecision in 18 passivity in 15 dependency and conscientiousness in 15 aggression and perfectionism in 12 and estheticism in 6 The Rorschach test was performed in all but 1 patient and revealed inability to respond to stimulation in the environment in 19 immaturity and anxiety in 18 guilt lack of flexibility in thinking and lack of ambition in 17 indecision and hostility in 13 excessive phantasy life in 11 aggression and passivity in 9 perfectionism in 12 and psychotic trends in 1 Study of the early developmental factors showed considerable emotional illness in the family major disturbances in the parent child and sibling relationships and many early traumatic experiences not specifically related to the intestinal tract

These studies do not disclose the reason for localization of the pathophysiologic process in the colon Obviously none of these personality traits when taken alone is specific for ulcerative colitis The understanding of such traits may be useful in treatment of these patients

Significance of Hyperalimentation in Treatment of Chronic Idiopathic Ulcerative Colitis Thomas E Machella[1] (Hosp of Univ of Pennsylvania) compares results obtained in treat

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(1) Am J Med 7 191 197 A gust 1949

fusion is maintained for 48 72 hours postoperatively if salt intake by mouth is insufficient Each urine specimen is tested for chlorides a reading of 4-6 Gm /L being considered satis factory The danger of overdosage is prevented by study of the fluid chart A full normal diet with plenty of roughage is suitable for most patients

Of 21 patients operated on since 1939 6 died 2 after opera tions performed in extremis 3 of intestinal obstruction and 1 probably as a result of salt depletion Complications included intestinal obstruction in seven patients and prolapse in four In the last nine operations during which the modifications in technic were developed only one death occurred The improved results are attributed to careful selection and preparation of the patient maintenance of an adequate salt balance and modi fication in technic Patients treated with ileostomy and fitted with the new bag show almost immediate improvement in nu trition and in mental and physical well being There is no evidence to prove that the colon will be restored to normal or closure of the ileostomy become practical

[Indications for surgery must be carefully evaluated because the ile ostomy will probably be permanent and ultimate results of operation are frequently uncertain However it is true that dramatic improvement in the patient s condition frequently follows ileostomy The suggestion of Dragstedt and his co-workers (Ann Surg 114 653 662 October 1941) of skin grafting the iliac stoma at the time it is made has eliminated much of the risk of the operation and has made it less of a handicap for the patient —Ed]

Effect of Vagotomy on Human Colon is described by Wil liam J Grace Cranston W Holman Stewart Wolf and Har old G Wolff[3] (Cornell Univ) The function of the human colon before and after bilateral supradiaphragmatic bilateral vagotomy performed as a therapeutic procedure for ulcera tive colitis was studied in a fistulous subject with a large area of evaginated colonic mucosa Before operation intravenous injection of 20 units of regular insulin was followed by a rapid increase in gastric acidity but 30 days postoperatively repetition of the test produced no increase Subcutaneous in jection of 0 0002 Gm prostigmin® resulted both before and after operation in increased blood flow contractility and mo tor activity of the evaginated colon

Control observation showed a relatively hyperactive bowel during discussion of relevant personal conflicts The mucosa

(3) G t t l gy 13 536 546 D emb 1949

patient Much of the dread of ileostomy has been overcome by use of the Koenig Rutzen bag (Fig 136) which does not interfere with the patient s ordinary daily activities Made of thin rubber it closely surrounds the proximal stoma by means of a thin rubber coated metal disk perforated for exact fit An easily removable solution of rubber latex applied to both skin and bag attachment insures watertight union A thin girdle to which the bag is attached affords additional support The contents can be emptied at will through an opening in



Fig 136—Ileostomy bag in position (Courtesy of Hardy T L. *et al* Lancet 2 59 July 2 1949)

the dependent part of the bag which is closed by a rubber band A second and larger bag is supplied for night use

In addition to psychologic preparation preoperative care includes a full high calorie high vitamin low residue diet and repeated blood transfusions X ray studies of the small intestine and occasionally fat balance tests determine ileo jejunal function Dietary salt is increased by 3-6 Gm daily Immediately before operation physiologic saline is given intravenously The ileal contents are sterilized by an insoluble sulfonamide preparation Penicillin is reserved for postopera tive infection should it occur Complete diversion of the ileal stream by a method adaptable to the special bag is the guid ing principle of operative technic The authors followed Cat tell s method with certain modifications Intravenous saline in

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became engorged and the bowel contracted but when the conversation was abruptly changed to divertive topics the colon blanched and became less contractive After vagotomy such effects were still readily demonstrable Before operation ingestion of a meal was accompanied by a rapid increase in motor activity blood flow and secretion in the colon These changes also occurred postoperatively The lysozyme concentration of the colonic secretion pre and postoperatively remained unchanged

Apparently vagotomy did not alter the function of the colon in this patient This suggests but does not prove that the vagus nerve in this patient does not innervate the cecum and ascending colon Colon reactivity and its capacity to develop an acute exacerbation of ulcerative colitis were not impaired by bilateral vagus section

[Although these conclusions are based on observation of only one patient they raise the question of the rationale of vagotomy for chronic ulcerative colitis The operation was first introduced as a therapeutic procedure by Dennis and Eddy in 1947 Subsequently Dennis and his associates reported results in 25 patients 14 of whom were significantly improved (Ann Surg 128 479-496 September 1948) A final appraisal of the procedure is not yet possible —Ed]

Treatment of Acute Proctologic Conditions Acute disorders of the anorectal and perianal regions are usually characterized by severe pain The anorectum is constantly subjected to trauma during evacuation and is an ideal site of entry for fecal pathogens Among acute proctologic conditions that require prompt treatment Emil Granet[4] (New York City) lists external thrombotic hemorrhoids thrombotic prolapsed strangulated internal hemorrhoids anal fissure anal perianal and pilonidal abscess coccygodynia acute venereal proctitis primary anal syphilis and fecal impaction These *conditions are diagnosed by the history plus scrupulous inspection and digital examination*

Thrombosed external hemorrhoids are best treated conservatively when the thrombus is small or when the patient seeks medical aid after resolution has begun Such treatment consists of application of witch hazel and water dressings to the involved area Ointments and suppositories are superfluous If the thrombosed mass is large solitary and seen early *surgical excision in the office is advised*

For early unilateral prolapsed strangulated thrombotic

(4) Am Pract 3 533 538 May 1949

and necrotic internal hemorrhoids a ligature type operation is performed When seen late or when the lesion completely encompasses the anus conservative therapy is instituted con sisting of rest in bed with the foot elevated constant wet witch hazel dressings sedatives and enemas With extensive slough ing 300 000 units of penicillin and 1 Gm streptomycin are advisable for several days After 10 20 days hemorrhoidec tomy is essential to prevent recurrence

Fissure in ano denotes a defect through the anal skin ex tending into the underlying subcutaneous sphincter muscle Tearing burning pain and sphincter spasm are the outstand ing symptoms Treatment of the early acute stage consists in relieving the sphincter spasm Anesthesia and relaxation are produced by injecting the sphincter muscles and perianal skin with 1 per cent procaine About 3 cc of a 0 5 per cent solu tion of diperodon hydrochloride is then injected under and around the fissure and an additional 7 cc into the sphincter muscle Sphincter relaxation persists for several days and permits healing Warm sitz baths and cleansing rectal irri gations are adjuvants For chronic anal fissure radical ex cision is the only curative treatment

Patients with acute cryptitis complain of a sensation of burning and aching in the anus aggravated after defecation and often associated with sphincter spasm Palpation of a localized tender induration is suggestive of acute cryptitis Treatment is medical consisting of hot sitz baths or douches small enemas and the instillation of an anesthetic antiseptic ointment in the rectum several times daily To prevent abscess formation 300 000 units of penicillin and 1 Gm streptomycin are given daily for several days

Perianal abscess includes all types of infralevator ab scesses The source of infection is usually found in the crypt tubule or intramuscular gland at the anus Incision and drain age plus removal of the source of infection will tend to pre vent occurrence of a fistula in ano

Acute pilonidal cyst abscess is common Simple incision and drainage performed early will relieve pain and minimize the extent of spread Definitive operation consisting of un roofing and saucerization of the side of the abscess should follow after one or two days

The etiologic factor in coccygodynia is considered to be

trauma from falls on the sacrococcygeal region or from parturition and occasionally anorectal surgical procedures Granet believes that pain in this condition results from tonic spasm of the pelvic muscles and in some instances from levator coccygeus bursitis Treatment consists of repeated finger massage of the paracoccygeal muscles in an effort to relieve the pain producing spasm

Acute anorectal venereal disease occurs as proctitis due to lymphopathia venereum or gonorrhea and as anal ulcers due to primary syphilis Prolonged intensive sulfadiazine therapy will cause resolution of *most cases of lymphopathia venereum Aureomycin may be of value Response to adequate* penicillin therapy in gonorrheal proctitis is prompt Clinical manifestations of primary syphilis of the anus are bizarre the commonest primary lesion being a superficial erosion at the anal edge with indurated edges and inguinal adenopathy Intensive penicillin therapy is indicated

Fecal impactions are common in the habitually constipated the senile bedridden invalids and depressive psychotics Treatment consists of manual disruption and fragmentation of the obstruction followed by an oil enema and after eight hours by repeated soapsuds enemas

Method of Improving Function of Bowel Use of Methyl cellulose According to J Arnold Bargen[5] (Mayo Clinic) the normal gradient of the intestinal tract may be upset in many ways Malignant and inflammatory diseases nervous tension and improper dietary habits may so interfere that anorexia vomiting diarrhea or constipation results Constipation is probably the commonest complaint In general it is caused by nervous fatigue and tension improper fluid intake improper dietary habits failure to respond to call to stool lack of exercise and excessive use of laxatives Correction logically lies in a suitable adjustment of these factors Any diet for relief of constipation must provide material which will add bulk Since it is difficult for many persons to secure adequate amounts of bulk producing foods in recent years a number of hydrophilous colloids have been added to the diet Methyl cellulose has been found helpful in irritable bowel associated with either constipation or diarrhea in intestinal stomas and in milder forms of intestinal infections associated with diar

(5) Ga t oent r logy 13 7[5] 9 Oct be 1949

rhea It is a white fluffy cotton like material which dissolves in water to form a colloidal solution A 0 5 Gm tablet in 1 oz lukewarm water dissolves in 5 10 minutes leaving many tiny translucent gelatinous particles It will pass through the digestive tract unchanged Animal studies suggest that ingested methylcellulose remains liquid throughout most of its passage through the digestive tract bulk does not begin to form until material reaches the lower part of ileum and colon

Many patients with irritable bowel and/or constipation and diarrhea obtained relief on 4 tablets of methylcellulose orally every four hours Twenty patients with sigmoid stomas and diarrhea and 6 with ileac stomas and diarrhea received 6 tablets four times daily with notable improvement in consistency of stools and reduction in their number Jelly like particles were seen floating in a liquid stool of four patients with high ileac stomas This observation tends to confirm the findings in animals the solution jells as it passes down the digestive tract In several cases of regional ileitis rectal stools changed from loose watery discharges to soft jelly like discharges However in cases of advanced ulcerative colitis in which much of the large bowel was damaged change was insignificant In some cases there was no change possibly because the intestinal content passed too rapidly to allow the necessary change in methylcellulose

Probably after initial control of intestinal activity a smaller amount of methylcellulose will continue the early satisfactory results As little as 2 tablets daily has been found to maintain normal function Methylcellulose does not constitute a cure for the intestinal dysfuncti ns discussed but it represents a valuable addition to a well ordered program of medical care

Chronic Ulcerative Colitis and Carcinoma are discussed by William G Sauer and J Arnold Bargen[6] (Mayo Clinic) Of 41 patients 21 were women and 20 men Mean age at onset of colitis was 26 5 years and at the time of diagnosis of complicating carcinoma it was 43 3 years A change in the nature of abdominal pain cramps or bowel habits increased bleeding or a palpable abdominal or rectal mass should arouse suspicion of a complicating neoplasm

Chronic active disease with few remissions characterized

(6) J A M A 141 98 986 D 3 1949

the course in 27 patients 10 had periodic exacerbations with periods of relative freedom from symptoms for as long as eight years

The 41 patients had 58 separate malignant lesions According to Broders classification 23 malignancies were grade 1 15 grade 2 7 grade 3 and 13 grade 4 Carcinomas occurred in the rectum in 19 patients and in the cecum in 10 The remaining lesions were distributed almost equally through the other portions of the colon

It is urged that patients with long standing chronic ulcerative colitis with or without ileostomy be periodically checked for malignant neoplasms

[In a recent study of local complications in 2 000 cases of chronic ulcerative colitis Sloan Bargen and Baggenstoss (Proc Staff Meet., Mayo Clin 25 240 244 May 10 1950) found presumptive evidence that neoplastic lesions developed in the colon or rectum in 107 (5 + per cent) There was acceptable proof in 88 cases In their opinion the true incidence was probably higher than the presumptive evidence indicated The mean duration of symptoms of chronic ulcerative colitis before the diagnosis of neoplasm was 18 years —Ed]

Carcinoma of Large Bowel Analysis of Clinical Features in 478 Cases, Including 88 Five Year Survivors, was made by Julian W Buser Joseph B Kirsner and Walter L Palmer[7] (Univ of Chicago) There was no relation between prognosis and age sex or duration of symptoms Pain was the most frequent symptom occurring in 69 8 per cent of patients Rectal bleeding next in frequency was described by 60 7 per cent It was commonest in carcinoma of the rectum and rectosigmoid Though gross bleeding is of considerable importance in diagnosis of cancer of the colon and rectum the significance of occult blood in the stool may be overemphasized Weight loss and anemia were frequent findings

Of the 267 patients who had one or more x ray examinations of the bowel a correct positive diagnosis was made in 94 per cent Of the tumors not detected by x rays 15 were located in the rectum or rectosigmoid and 1 in the sigmoid proper The superiority of the proctoscope to x rays in detecting rectal and rectosigmoid lesions is generally recognized Considering 15 cm the upper limit of the rectosigmoid there were 276 cases with lesions at or distal to that level and well within reach of the proctoscope However after careful evaluation of all 478 cases x rays can be considered de-

(7) C r 3 214 2 8 Ma ch 1950

cisive and indispensable diagnostic tools in one third of the cases

Incidence of survival of patients with rectal tumors was 21 6 per cent in those with tumors in the remainder of the colon it was 39 5 per cent Apparently the chance of survival was considerably better when the tumor was in the colon particularly in the right half than when it was in the rectum or rectosigmoid The resectability rate slightly lower in lesions of the rectum does not offer sufficient explanation for the high number of failures in this group Delay in diagnosis or delay in onset of symptoms may be important prognostic factors

Metastases were found at the time of original diagnosis or subsequently at operation in 230 patients and 19 had metastases in two or more general areas More than one third of the patients had generalized abdominal metastases as the first manifestation of recurrence In three patients metastases were treated by further surgery and all are living 7 17 years postoperatively

In 302 patients with carcinoma of the colon or rectum diagnosed or treated before 1944 the survival rate varied from 25 6 to 57 1 per cent depending on the selection of cases and the manner in which statistics were handled Probability of recurrence diminishes sharply two years after resection Of patients who accepted the advice of the attending physician approximately one third were alive and well five years later

Recurrent vs New and Independent Carcinomas of Colon and Rectum J W Long Charles W Mayo Malcolm B Dockerty and Edward S Judd Jr [8] consider a recurrent carcinoma one which developed from cells which were part of the original cancer or secondary colonies which were not removed at operation A new primary carcinoma is one which developed from cells which were not malignant at the time the original carcinoma was removed and hence not a part of that carcinoma Of 30 patients studied 21 had actual persistence of the original carcinoma and 9 exhibited new and independent carcinomas Grossly and microscopically the recurrent carcinomas pushed up underneath the muscularis mucosae and mucosa to push these structures aside or infiltrate them but they exhibited no transitional zone between carcinoma and

(8) P oc Staff M t M y Cl 25 169 178 Ap 12 1950

normal mucosa For those with recurrent lesions an average of 2 9 years elapsed between operations and the mean survival time after recurrence was 1 5 years In those with new and independent carcinomas there was a transitional zone at the junction of the mucosa and the tumor The so called normal glands at the tumor margin were made up of cells with dark staining nuclei which tended to migrate away from the basement membrane In general the picture was that of carcinoma in situ as described by Broders Even in high grade lesions there was no distinct boundary between mucosa and cancer In the six patients who could be traced the mean interval between operations was 4 1 years and the mean survival time 5 4 years

Patients suspected of having recurrent carcinomas of the colon or rectum should not be denied the benefit of surgical exploration if there is no evidence of distant metastases In this study the prognosis of patients with new and independent carcinomas was excellent A larger series must be studied before it can be determined what percentage of suspected recurrent carcinomas will prove to be new and independent carcinomas

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